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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. NATURAL ANTIBODIES TO THE HUMAN T CELL LYMPHOMA VIRUS IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA.

Posner LE, Robert-Guroff M, Kalyanaraman VS, Poiesz BJ, Ruscetti FW, Fossieck B, Bunn PA, Minna JD, Gallo RC
Lab. Tumor Cell Biology, NIH, Bethesda, MD, 20205
J Exp Med; 154(2):333-346 1981

Serum samples were obtained from patients with cutaneous T cell lymphoma (CTCL) and leukemia, and from 55 normal random donors. Retroviruses HTLV-CR (grown in HUT 102 cells) and HTLV-MB, isolated from patients CR and MB, re-

HE 20.3173/2:

spectively, were used, along with several other retroviruses. The sera were screened for the presence of natural antibody to HTLV-CR, using a solid-phase radioimmunoassay. Sera from patient CR and one other patient reacted specifically with proteins of HTLV-CR. CR serum also react ed with HTLV-MB proteins. Solid-phase immunocompetition and competition radioimmunoprecipitation assays demonstrated the specificity for HTLV-CR proteins. Patient CR antibodies were directed against viral core proteins with mol wt of 24,000 and 19,000, as shown by radioimmunoprecipitation analysis. Some reactivities to other animal retroviruses, including the baboon endogenous virus, simian sarcoma virus, feline leukemia virus, and gibbon ape leukemia virus, were demonstrated. These reactivities apparently were not virus-specific, but related to cellular antigen contamination of viral preparations or to antigens in fetal calf serum. The results indicate for the first time a specific antibody reaction to a retrovirus in humans. (38 Refs)

2. CORONAVIRUS-ASSOCIATED ANTIBODIES IN NASOPHARYNGEAL CARCINOMA AND INFECTIOUS MONONUCLEOSIS.

Arnold W, Klein M, Wang JB, Schmidt WAK, Trampisch HJ
Dept. Otorhinolaryngology, Klinikum Grosshadern, Marchioninstrasse 15, D-8000 Munich 70, W. Germany
Arch Otorhinolaryngol (NY); 232(2):165-177 1981

Particles in the cytoplasm of nasopharyngeal carcinoma (NPC) cells were found which resembled coronaviruses. To determine the nature of these particles serum titer determinations were performed in NPC patients, infectious mononucleosis patients, and a control group. Epstein-Barr nuclear antigen (EBNA) test were made on tumor cells from NPC tissues and cells from cultures infected with coronaviruses. For immunological identification of coronavirus, the human coronavirus strain 229E was cultured on human fetal lung fibroblast MRC-C cells. Comparison of antibody levels showed clearly higher levels of IgG in NPC patients than in controls. IgA was the same in either group. IgM titer was in the low range in NPC patients. Infectious mononucleosis patients showed similar tiers to the NPC patients. The EBNA test was positive in all NPC cells, negative in cell cultures infected with coronavirus. In immunofluorescence tests serum from NPC patients produced intense fluorescence when applied to coronavirus-infected cells. Known high-titer coronavirus sera did not produce a similar result in MRC cells not infected with coronavirus. Evidently coronaviruses are present in the cytoplasm of NPC tumor cells. A correlation between the RNA coronavirus and the Epstein-Barr virus suggests a possible interaction between them as a factor in NPC. (35 Refs)

3. POSSIBLE ASSOCIATION BETWEEN ONCOGENIC VIRUSES AND HUMAN BREAST TUMORS.

Il'in KV, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):10-18 1981

Literature data on the association between human breast tumors and at least two oncogenic viruses are reviewed. Immunodiffusion with autoradiography showed the presence of protein with antigenic determinant similar to that of antigen p27 in 11/23 breast fibroadenoma specimens. The speci mens of malignant breast tumors did not contain the antigenic determinant of simian virus type D. The specimens of human breast carcinoma were found to contain the antigen similar to the major envelope protein gp52 of murine virus of mammary gland. The presence of gp52 antigen was not correlated either with the age of the patient or with the histology of the tumor. (48 Refs) (In RUS)

4. CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY OF GYNECOLOGIC TUMORS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Clinical Immunology and Immunotherapy of Gynecologic Tumors (Cancer Overview) Freedman, R S, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922802:; OT-81/02:52pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Overview includes all clinical aspects of the immunology and immunotherapy of gynecologic tumors. Immunologic studies of gestational trophoblastic disease include paternal antigen expression, human leukocyte antigen histocompatibility, and immunoassays of betaglycoprotein and human chorionic gonadotropin (HCG). Antigenic studies of the uterine cervix include herpes viruses, cytomegaloviruses, tumor-associated antigens, carcinoembryonic antigens and beta oncofetal antigens. Studies of cellular immune response, lymph node morphology and lymphocytic infiltration as prognostic indicators of the uterine cervix are covered as well as the effects of radiotherapy on the immune status of patients with cervical carcinoma. Immunologic aspects of ovarian tumors which are covered include human ovarian tumor-associated antigens and oncofetal antigens. Non-specific, active specific, and other immunotherapeutic trials in gynecologic neoplasms are also included in this Overview.

5. HERPESVIRUS-INDUCED ANTIGENS IN SQUAMOUS-CELL CARCINOMA IN SITU OF THE VULVA.

Kaufman RH, Dreesman GR, Burek J, Korhonen MO, Matson DO, Melnick JL, Powell KL, Purifoy DJ, Courtney RJ, Adam E
Dept. Obstetrics and Gynecology, Baylor Coll. Medicine, Houston, TX, 77030
N Engl J Med; 305(9):483-488 1981

Tissue and serum specimens from 19 patients (24-79 yr old) with squamous-cell carcinoma (SCC) in situ of the vulva (10 patients), severe dysplasia (1), condyloma acuminatum (4), and controls seen for periodic check-up (4), were evaluated for herpes simplex virus Type 2 (HSV2) DNA-binding proteins. Nine of 10 biopsy specimens from patients with SCC or severe dysplasia reacted strongly when stained with an ti-ICPS34/35 (rabbit antiserum to HSV2-infected-cell-specific protein 34/35), and eight also reacted with anti-VP143 (rabbit antiserum to nonstructural HSV2 protein); five also reacted with anti-ICSP11/12 (rabbit antiserum to HSV2-infected-cell-specific protein 11/12). All the positive reactivity observed with anti-ICSP34/35, anti-ICSP11/12 and anti-VP143 was localized in the cytoplasm rather than the nuclei, as has been previously reported in infected cells. Whole-virion structural antigens were not observed, although serological evidence of previous HSV2 infection was found in patients tested for the presence of antibodies. Serum antibodies to HSV2 were noted in nine patients with SCC, including one with mild dysplasia, and two with normal tissue. The parallel rise in the incidences of HSV2 infection and of vulvar SCC in situ and the demonstration of HSV2-specific proteins in this tissue suggest an association of HSV2 infection with this cancer. (17 Refs)

6. IMMUNOPEROXIDASE LOCALIZATION OF PAPILLOMAVIRUS ANTIGENS IN CERVICAL DYSPLASIA AND VULVAR CONDYLOMAS.

Kurman RJ, Shah KH, Lancaster WD, Jenson AB
Dept. Obstetrics and Gynecology, Georgetown Univ. Hosp., 3800 Reservoir Road, Washington, DC, 20007
Am J Obstet Gynecol; 140(8):931-935 1981

Biopsies of 50 cases kf cervical dysplasia (46 &ild and 4 moderate) and 40 cases of vulvar condyloma acuminata (genital warts) were screened for the presence of papillomavirus antigens by means of a peroxidase-antiperoxidase method having immunospecificity against the genus-specific (common) antigen(s) of the papillomaviruses. With the use of this technique, on formalin-fixed, paraffin-embedded tissue, papillomavirus antigens were detected in cells with cytologic and histologic features of wart virus infection (so-called koilocytotic atypia). Cells showing a positive reaction for papillomavirus antigens were identified in 24 of 50 (48%) cases of cervical dysplasia and 20 of 40 (50%) cases of vulvar condyloma. The results of this study provide specific confirmation of the presence of papillomavirus antigens in cervical dysplasia and suggest that the papillomavirus may be an important factor in the etiology of this disease. (Author abstract) (18 Refs)

7. ASSOCIATION OF EPSTEIN-BARR VIRUS WITH NASOPHARYNGEAL CARCINOMA IN ALASKAN NATIVE PATIENTS: SERUM ANTIBODIES AND TISSUE EBNA AND DNA.

Lanier AP, Bornkamm GW, Henle W, Henle G, Bender TR, Talbot ML, Dohan PH
Alaska Investigation Div., Centers for Disease Control, 225 Eagle St., Anchorage, AK, 99501
Int J Cancer; 28(3):301-305 1981

Biopsy specimens from Alaskan Native patients with nasopharyngeal carcinoma (NPC) and from other patients seen on the otolaryngology service were tested for Epstein-Barr virus-specific DNA and nuclear antigen (EBNA). Serum samples from both groups were tested for various EBV-related antib odies. EBV DNA and EBNA results were in agreement in 29 of 31 tissue specimens tested by the two methods. Ten of 11 biopsies containing NPC cells were positive for EBV DNA. Two NPC patients had biopsies that showed only atypical epithelium but were also positive for EBV DNA or EBNA. The other tissue specimens were negative except for biopsies from two patients: one with a parotid gland lymphoepithelial lesion; another with undifferentiated carcinoma of salivary gland origin. (Author abstract) (28 Refs)

8. CYTOPLASMIC EXPRESSIONS SEEN IN HEPATOCELLULAR CARCINOMA.

Nakanuma Y, Sugiura H, Ohta G
Second Dept. Pathology, Sch. Medicine, Kanazawa Univ., Kanazawa-shi, Ishikawa Pref. 920, Japan
Kanzo; 22(2):266-273 1981

The frequency and degree of occurrence of eight cytoplasmic expressions in carcinoma cells of minute and huge hepatocellular carcinoma (HCC) were determined. Fat accumulation, orcein-positive granules (but neither hepatitis B surface antigen nor copper-containing granules), iron stain-positive granules, and Mallory's hyaline were seen more frequently in minute HCC than in huge HCC (p less than 0.001), indicating that the expression-positive cells appear in the early stage of HCC and may be mostly replaced by negative cells in huge HCC. Bile plugs and globular hyaline, however, were frequently seen in huge as well as in minute HCC (p greater than 0.3), indicating that they are rather persistent cytoplasmic expressions of HCC throughout the entire course. Clear-cell transformation and ground-glass change of carcinoma cells were rarely seen, with no difference in frequency between the two types of HCC. (Author abstract) (24 Refs) (In JPN)

9. REACTIVITY OF ANTISERA TO ANTIGENS OF C-TYPE VIRUSES WITH LEUCOCYTES FROM PATIENTS WITH ACUTE LEUKAEMIA.

Pullen S, Hersey P
(c/o Hersey) Kanematsu Memorial Inst., Sydney Hosp., Macquarie St., Sydney, Australia 2000
Pathology; 13(2):289-298 1981

A number of previous studies have suggested that certain C-type viruses from non-human primates are associated with acute leukemia in humans. The present study sought to examine this association further by detection of antigens related to these viruses on the surface of acute leukemia cells. Antisera against the whole viruses or the major internal protein of simian sarcoma, endogenous baboon and Rauscher viruses were tested against mononuclear cells from patients with acute leukemia at various stages of their disease in 51Cr release WBC dependent cytotoxic assays. A high proportion of the patients had antigens related to these viruses detectable on their blood WBC at some stage in their disease whereas with one exception blood WBC from non-leukemic subjects did not. The expression of these antigens did not show a close relation to the number of blast cells in blood detected on morphological grounds. Antigens relat ed to the non-human primate viruses were detected on mononuclear cells from bone marrow samples of several non-leukemic patients which indicated they were not specifically associated with leukemia. Antigens related to the Rauscher virus were detected on cells of practically all bone marrow samples tested. These results suggest that assays to detect these antigens would be of limited usefulness to monitor disease activity in patients with acute leukemia. Their expression on blood WBC however appeared strongly associated with acute leukemia and further studies to assess the prognostic and epidemiological significance of detection of these antigens appears warranted. (Author abstract) (16 Refs)

10. FAMILIAL ACUTE MYELOGENOUS LEUKEMIA ASSOCIATED WITH RNA VIRUS AND POLYMORPHISM OF 1QH+.

Sadamori N, Nonaka H, Ichimaru M, Igarashi H, Hirota M, Sawada H
Dept. Genetics and Endocrinology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(1):23-30 1981

In order to investigate the genetic background of leukemogenesis of two brothers with acute myelogenous leukemia (AML), they and their family members were studied geneticall-ly, immunologically, virologically, and cytogenetically. Their parents were first cousins once removed and had the same or a very close type of human WBC antigen (HLA) and blood groups. In all five non-leukemic family members the IgG level was elevated, and in two healthy siblings the IgM level was beyond the normal range. The RNA reverse transcriptase activity in serum of the younger brother (Case 2) with AML was elevated. A cytogenetic study of the family revealed polymorphism of 1qh+. Based on these findings, we discuss the genetic and environmental factors of familial leukemia. (Author abstract) (24 Refs)

11. NONDETECTION OF INFECTIOUS HEPATITIS B VIRUS IN A HUMAN HEPATOMA CELL LINE PRODUCING HEPATITIS B SURFACE ANTIGEN.

Tabor E, Copeland JA, Mann GF, Howard CR, Skelly J, Snoy P, Zuckerman AJ, Gerety RJ
Bureau Biologics, 8800 Rockville Pike, Bethesda, MD, 20205
Intervirology; 15(2):82-86 1981

The PLC/PRF/5 human hepatoma cell line producing hepatitis B surface antigen (HBsAg) was studied to determine whether infectious hepatitis B virus (HBV) was also being produced. Two chimpanzees with no previous exposure to HBV and no serologic markers of past or active HBV infection were inoculated iv with 50 ml of either tissue culture supernatant fluid (357 ng/ml HBsAg) or a suspension of cells disrupted by repeated freeze-thaw cycles (57 ng/ml HBsAg). No evidence of HBV infection was detected in either chimpanzee during 6 mo of evaluation. This study suggests that the expression of a portion of the HBV genome, when a portion or all of that genome has been incorporated in a host cell, can result in the production o f HBsAg without infectious HBV. If it becomes possible to produce a similar expression of this portion of the genome by itself in nonmalignant cells. HBsAg without HBV may be produced in vitro for use in hepatitis B vaccines. (Author abstract) (21 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

12. HUMAN CELL TRANSFORMATION BY SIMIAN VIRUS 40. BIOLOGIC FEATURES OF CLONED LINES.

Sack GH, Obie C
Dept. Medicine, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Exp Cell Res; 134(2):425-432 1981

Nine lines of doubly cloned Simian Virus 40 transformed human fibroblasts have been isolated. Precrisis in vitro characteristics of growth rate, saturation density, T antigen expression, growth in methylcellulose suspension, protease production and infectious center formation were widely divergent, although distinct for individual lines. Lines with higher T antigen expression had higher growth rates and saturation densities but grew less well in methylcellulose. Chromosome counts in most proliferating lines were in the 38-48 range; one line had 67, whereas another, poorly growing line showed 22. No distinguishing chromosomal abnormalities were present. This biologic heterogeneity suggests distinct molecular differences underlying transformation in the lines and emphasizes the importance of considering various factors as indicative of the transformed state. (Author abstract) (33 Refs)

13. ANALYSIS OF THE NONVIRAL ANTIGENS IMMUNOPRECIPITABLE BY SV40 T ANTIBODY FROM SV40-TRANSFORMED HUMAN/MOUSE HYBRID CELL LINES.

Stitt DT, Mangel WF
(c/o Mangel) Dept. Biochemistry, Univ. Illinois, Urbana, IL, 61801
Virology; 114(1):149-160 1981

The expression of nonviral antigens, ie, host-coded proteins with mol wt from 48,000-56,000 (48K-56K) immunoprecipitable from extracts of simian virus 40 (SV40)-infected or -transformed cells by anti-SV40 tumor antibody, was examined in four SV40-transformed human cell lines, one SV40-transformed mouse cell line, and eight SV40-transformed human/mouse somatic cell hybrid cell lines produced by fusion of SV40-transformed human cells with untransformed mouse cells. Differences were found in the patterns of expression of these viral induced proteins among the human cell lines, between the human and the mouse cell lines, and between the human/mouse somatic cell hybrid cell lines and the human lines from which they were derived. Two of the human cell lines expressed only a 55K nonviral antigen; two expressed both a 55K and a 52K nonviral antigen. The mouse cell line expressed both a 55K and a 48K nonviral antigen. Each hybrid cell line expressed a 55K and also a 48K nonviral antigen, except one. The BALB IV-8 hybrid cell line expressed 55K and 52K nonviral antigens. By comparing the tryptic peptides fractionated on cation exchange colu mns of the nonviral antigens we determined: (1) the 48K nonviral antigen in human/mouse hybrids is encoded by a mouse chromosome. (2) The 52K nonviral antigen in the BALB IV-8 human/mouse hybrid is encoded by a mouse chromosome. It is possibly a precursor to the mouse 48K protein because it contains one extra tryptic peptide in addition to those of the mouse 48K protein, because one peptide has an altered mobility and because the 52K protein is found, so far, only in a human/mouse hybrid that does not exhibit a 48K nonviral antigen. (3) The 55K nonviral antigen in the C57-VII-6 human/mouse hybrid is encoded by a human chromosome. In the BALB IV-8 human/mouse hybrid, there is a 55K protein encoded by a human chromosome and probably a 55K protein encoded by a mouse chromosome. (4) If the gene encoding the human 55K nonviral antigen is located on a single chromosome, it is located on human chromosome 7. (Author abstract) (25 Refs)

14. SV40 ANTITUMOR SERA THAT DIRECTLY IMMUNOPRECIPITATE SMALL-T-ASSOCIATED CELLULAR PROTEINS.

Rundell K, Yang YC
Dept. Microbiology-Immunology, Northwestern Univ. Medical Center, 303 E. Chicago Ave., Chicago, IL, 60611
Virology; 114(1):297-301 1981

Two cellular proteins, 56K and 32K, are immunoprecipitated in association with SV40 small-t antigen using antisera from animals bearing SV40-induced tumors. Antitumor sera have now been identified that immunoprecipitate these proteins directly from uninfected, as well as infected, cells. (Author abstract) (10 Refs)

15. EXPRESSION OF SV40 T ANTIGEN IN FINITE LIFE-SPAN HYBRIDS OF NORMAL AND SV40-TRANSFORMED FIBROBLASTS.

Pereira-Smith OM, Smith JR
W. Alton Jones Science Center, Old Barn Road, Lake Placid, NY, 12946
Somatic Cell Genet; 7(4):411-421 1981

In order to determine the distribution of in vitro lifespans of hybrid cells resulting from the fusion of normal and Simian virus 40 (SV40)-transformed cells, a biochemical selection system utilizing ouabain and HAT (hypoxanthine, aminopterin, and thymidine) was used. When normal human fibroblasts that had ceased proliferation were fused with SV40-transformed fibroblasts, cell proliferation was reinitiated in the resultant hybrids. This occurred even when the senescent normal parent cells had ceased replicating and were nonproliferative for 6 mo. In about 70% of the hybrids, the induced proliferative ac-

tivity ceased within seven population doublings (PDs). In the remainder of the hybrid clones the proliferation was much more extensive (16-62 PDs). However, even these relatively long-lived hybrid clones eventually ceased proliferating. These results indicated that the processes that lead to in vitro senescence in normal cells can be reversed only temporarily by fusion with an SV40-transformed cell. UV irradiation appeared to impair the ability of SV40-transformed cells to reinitiate cell division. It was shown that the the hybrid clones which have limited division potential express viral T antigen. The hybrid clones seemed to contain viral DNA which was expressed, did not produce live virus, and continued to exhibit a limited lifespan. (24 Refs)

16. REPLICATION OF SIMIAN VIRUS 40 DNA IN NORMAL HUMAN FIBROBLASTS AND IN FIBROBLASTS FROM XERODERMA PIGMENTOSUM.

Ozer HL, Slater ML, Dermody JJ, Mandel M
Dept. Biological Sciences, Hunter Coll., City Univ. New York, New York, NY, 10021
J Virol; 39(2):481-489 1981

Simian virus 40 infection of semipermissive human diploid fibroblasts (HF), at early passage in cell culture, was compared with that of permissive established monkey cell lines. Viral DNA can be readily detected at 24 to 48 hr postinfection at 37 C with a high multiplicity of infection, approaching 10% of that of monkey cells (TC7). The length of time necessary for replication of an av molecule of viral DNA was found to be indistinguishable in HF and TC7 cells. Strand elongation plus termination were assessed by following the accumulation of DNA I at 40 C from replicative intermediates of tsA30 prelabeled at 33 C, obviating isotope pool problems. Combined initiation and elongation of wild-type viral DNA was measured by density shift experiments involving a 5-bromodeoxyuridine chase of prelabeled [3H]thymidine-labeled viral DNA. Determination of accumulation of viral T and V antigens supports the conclusion that the most likely basis for the reduced virus yield in HF cells results from the inefficiency of an early stage in virus infection, before or during uncoating. Similar results were obtained in fibroblasts derived from patients with xeroderma pigmentosum, suggesting that enzymes of uv repair are not required in unirradiated simian virus 40 DNA synthesis. (Author abstract) (34 Refs)

17. IMMUNOSELECTION OF SIMIAN VIRUS 40 LARGE T ANTIGEN MESSENGER RNAS FROM TRANSFORMED CELLS.

Oren M, Levine AJ
(c/o Levine) Dept. Microbiology, State Univ. New York Sch. Medicine, Stony Brook, NY, 11794
Virology; 113(2):790-793 1981

The messenger RNAs (m-RNAs) coding for the simian virus 40 (SV40) large tumor antigen were substantially purified by immunoprecipitation of polysome fractions from SV40-transformed cells. The level of SV40 T antigen m-RNA in the transformed cell used in this study was estimated at 0.05% of the total population of polyadenylated m-RNAs and a several-hundred-fold purification of this m-RNA was achieved by employing antibodies to SV40 large T antigen purified by either of two methods. The procedures described in this communication should be particularly useful for the immunoselection and purification of low-abundance m-RNAs or when the antigen is not available in large quantities. (Author abstract) (12 Refs)

18. SV40 GENE EXPRESSION IS MODULATED BY THE COOPERATIVE BINDING OF T ANTIGEN TO DNA .

Myers RM, Rio DC, Robbins AK, Tjian R
Dept. Biochemistry, Univ. California, Berkeley, CA, 94720
Cell; 25(2):373-384 1981

We analyzed the DNA binding properties of wild-type simian virus 40 large T antigen and found that the protein binds cooperatively to three tandem sites at a regulatory region of SV40 DNA. One consequence of this T antigen: DNA interaction is the specific repression of SV40 early RNA synthesis in vitro. We mapped a region of 85 base pairs that is necessary and sufficient to initiate early SV40 transcription in vitro. This promoter region lies directly adjacent to the third T antigen binding site but does not include the 'TATA' sequence. To determine how T antigen interacts with its binding sites to repress RNA synthesis, we analyzed transcription directed by a variety of wild-type, mutant and hybrid template DNAs. Our findings suggest that the cooperative binding of T antigen to its sites is directly responsible for inhibiting the initiation, rather than blocking elongation, of early RNA synthesis. A model is presented to explain the role of T antigen binding in the regulation of viral transcription and DNA replication during SV40 lytic infection. (Author abstract) (68 Refs)

19. CHARACTERIZATION OF A GENE ENCODING A 115 K SUPER T ANTIGEN EXPRESSED BY A SV40-TRANSFORMED RAT CELL LINE.

May E, Jeltsch JM, Gannon F
Institut de Recherches Scientifiques sur le Cancer, B.P. no 8, 94800 Villejuif, France
Nucleic Acids Res; 9(16):4111-4128 1981

It has been reported that SV40-transformed V 11 F 1 clone 1 subclone 7 rat cells (subclone 7) produce a super T antigen of 115,000 M. This super T antigen is entirely SV40 coded and is synthesized by translation of an elongated form of SV40 early mRNA. The results reported here show that there is only one independent insertion of viral DNA in the cellular genome of subclone 7 cells. When DNA from subclone 7 cells was cleaved with Bam HI endonuclease two distinct SV40 sequence containing fragments were generated with sizes of 5 Kb and 10 Kb, respectively. Two recombinant cosmids were constructed by insertion of the 5 Kb and 10 Kb fragments, respectively, into cosmid pHC 79. Using restriction map analysis and nucleotide sequencing, we showed that the 5 Kb fragment actually contained the complete sequence of a gene encoding super T antigen. As compared to the normal SV40 early gene, the sequence of super T gene showed the following rearrangements: (i) The segment between nucleotides 4116-3544 was duplicated in a direct order and (ii) these two copies of 573 nucleotide sequence were separated by a 93 nucleotide tract which was a nearly perfect inverted repeat of the segment located between nucleotides 4868 and 4776 (nucleotide numbering used here = Weissmann number + 17). (Author abstract) (30 Refs)

20. MONOCLONAL ANTIBODIES SPECIFIC FOR SIMIAN VIRUS 40 TUMOR ANTIGENS.

Harlow E, Crawford LV, Pim DC, Williamson NM
Dept. Molecular Virology, Imperial Cancer Res. Fund Lab., London WC2A 3PX, England
J Virol; 39(3):861-869 1981

Thirty hybridomas that secrete Ig against the simian virus 40 tumor antigens were isolated and cloned. Of these, 28 produced antibodies which bound to simian virus 40 large-T, and

2 produced antibodies which bound to the host 53,000-dalton protein. As in previous work, large-T antigen was found to have at least one determinant that it shared with small-t antigen and to have a minimum of six unique determinants. Several of the monoclonal antibodies from the L series hybridomas recognized determinants that were present on a subset of the large-T antigen from simian virus 40-transformed mouse cells. These monoclonal antibodies should be useful in studies of the structure and function of the simian virus 40 tumor antigens. (Author abstract) (30 Refs)

21. FUNCTIONS OF T ANTIGENS OF SV40 AND POLYOMAVIRUS.

Hand R

McGill Cancer Centre, McGill Univ., 3655 Drummond, Montreal, Quebec, H3G 1Y6, Canada

Biochim Biophys Acta; 651(1):1-24 1981

Functions of the tumor or T antigens of SV40 and polyomavirus are reviewed. Topics discussed include genome organization (SV40 genome, polyomavirus genome, and comparison of maps), proteins of the early regions (SV40 antigens, polyomavirus T antigens, and super T antigens), functions of T antigens (small t antigen, middle T antigen, and large T antigen), other immunoreactive T antigens (tumor-specific transplantation antigens, U antigen, and cellular proteins bound by antibodies against SV40 T antigens), large T antigen binding to DNA, viral DNA synthesis, cellular DNA synthesis (SV40 and polyomavirus), adenovirus helper function, regulation of viral transcription, integration of viral DNA, enzyme reactivities associated with T antigens (SV40 and polyomavirus), T antigens and transformation (SV40, polyomavirus, and A and N transformants), and conclusions. (196 Refs)

22. CLONING AND CHARACTERIZATION OF THE INTEGRATED VIRAL DNA FROM THREE LINES OF SV40-TRANSFORMED MOUSE CELLS.

Clayton CE, Rigby PW

Cancer Res. Campaign, Eukaryotic Molecular Genetics Res. Group, Imperial Coll. Science and Technology, London SW7 2AZ, England

Cell; 25(2):547-559 1981

Recombinant DNA techniques have been used to isolate the integrated viral DNA, together with flanking cellular sequences, from three independently isolated lines of SV40-transformed BALB/c 3T3 cells. We have determined the structures of these cloned segments and their relationships to one another by restriction enzyme mapping, electron microscopic heteroduplex analysis and transfer hybridization experiments. Our data indicate that the structure of the integrated viral DNA is consistent with the i dea that integration involves a tandemly repeated intermediate, that extensive amplification and rearrangement of viral and adjacent cellular sequences occurs after integration and that the majority of viral DNA insertions do not contain an intact early transcription unit. The altered templates presumably encode the truncated and super T antigens found in these cells. Either they are interrupted in the middle of the early region, in which case they generally retain the region in which tsA mutations map, or they contain tandem duplications of the tsA region. Further structural analysis will allow the prediction of the precise structures of these unusual T antigens, and the availability of the corresponding templates opens the way to an analysis of the functions of these proteins. (Author abstract) (52 Refs)

23. INDUCTION OF COMPLEMENT RECEPTOR EXPRESSION IN CELL LINES DERIVED FROM HUMAN UNDIFFERENTIATED LYMPHOMAS. II. CHARACTERIZATION OF THE INDUCED COMPLEMENT RECEPTORS AND DEMONSTRATION OF THE SIMULTANEOUS INDUCTION OF EBV RECEPTOR.

Magrath I, Freeman C, Santaella M, Gadek J, Frank M, Spiegel R, Novikovs L

Pediatric Oncology Branch, NCI, Bethesda, MD, 20205

J Immunol; 127(3):1039-1043 1981

We have studied the specificity of complement receptors induced by theophylline in two cell lines derived from undifferentiated lymphomas, one of Burkitt's type, and compared it to that of complement receptors in other cell types. Both C3b and C3d receptors were induced. The induced C3b receptor differed from the C3b receptor of mature normal lymphocytes, polymorphonuclear leukocytes and the cells of a nodular lymphoma in two respects. Firstly, it bound C3b much less avidly (by a factor of several hundred-fold) and secondly, we were unable to demonstrate C4b binding. EBV receptors were induced at the same time as complement receptors, and permitted the conversion of a greater fraction of cells to EBNA positivity after experimental infection with EBV. The induction of receptors was not associated with a change in the fluidity of the plasma membranes and our data do not favor a different orientation of induced receptors within the membrane as compared to receptors of other cell types - a potential explanation for the different specificities. Our findings are consistent with the possibility that the complement receptors of lymphocyte precursors differ from those of mature lymphocytes. (Author abstract) (20 Refs)

24. PROPAGATION OF B-LYMPHOTROPIC PAPOVAVIRUS (LPV) IN HUMAN B-LYMPHOMA CELLS AND CHARACTERIZATION OF ITS DNA.

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Virology; 114(1):228-235 1981

The B-lymphotropic papovavirus (LPV) isolated originally from African green monk ey (AGM) B-lymphoblasts has been adapted to growth in the human Epstein-Barr virus (EBV)-negative B-lymphoma line BJA-B by repeated passages within these cells. After 11 passages of virus approx 20-25% of the cells were infectible within a 6 day period. Except for an abortive infection of another EBV-negative human B-lymphoma line, Ramos, and the EBV-positive Raji line of Burkitt lymphoma origin, cells of all other human lines of lymphatic origin tested thus far proved to be refractory to this infection. Viral DNA isolated from the BJA-B adapted strain was compared to that from the original AGM isolate. Only minor modifications were demonstrable in the HaeIII cleavage pattern of both isolates. A BJA-B subline persistently infected with LPV was established after cocultivation of BJA-B cells with LPV-producing AGM lymphoblasts. About 0.5-15% of these cells synthesized viral antigens at various intervals of cultivation. Viral DNA isolated from these cells after 12 mo of persistent infection revealed a remarkable heterogeneity in size and in the cleavage pattern when analyzed with restriction endonucleases. Molecular cloning of this DNA in pBR 322 plasmid underlined this heterogeneity. The majority of clones obtained revealed deletions which preferentially mapped within the D-F fragments of the HaeIII map. (Author abstract) (21 Refs)

25. CLONING OF A DEFECTIVE POLYOMA DNA MOLECULE WITH REARRANGEMENTS IN THE REGION CODING FOR MIDDLE AND LARGE T ANTIGENS.

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FEBS Lett; 130(2):269-271 1981

To define the sequences of polyoma virus (Py) that are essential for cell transformation, defective Py DNA molecules were cloned in pBR322. The recombinant plasmids were tested for their capacity to transform rat 3T3 cells in culture. DNA from the polyoma virus strain ts-P155 was digested with HindIII and the fragments ligated in the HindIII site of pBR322 with T4 DNA ligase. To screen for defective molecules, the recombinant plasmids were selectively digested, and examined by agarose gel electrophoresis and endonuclease mapping. The Py DNA sequence in fragment df55 was found to be interrupted from approx 88-24 units before the HpaII-4/8 junction and the HindII site in HpaII-6. This deletion left the sequence encoding the small T segment intact but removed approx 1,800 base pairs (bp) from the large T antigen gene and about 530 bp from the middle T antigen gene. An interesting feature was the loss of approx 300 bp from the C-terminal portion of the middle T antigen gene. Transfection of 3T3 cells with df55-containing recombinant plasmids failed to transform cultured cells kept for periods up to 3-4 wk at 39 C. The inability of pHdf55 to transform was ascribed to the absence of a functional middle T antigen. While not excluded, the small T an tigen alone was not thought capable of inducing expression of the transformed phenotype. (16 Refs)

26. LOSS OF FUNCTIONAL LARGE T-ANTIGEN AND FREE VIRAL GENOMES FROM CELLS TRANSFORMED IN VITRO BY POLYOMA VIRUS AFTER PASSAGE IN VIVO AS TUMOR CELLS.

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J Virol; 39(2):422-431 1981

We have analyzed the state, arrangement, and expression of polyoma viral DNA sequences in a number of in vitro-transformed Fischer rat cells before and after growth in vivo as tumor cells. When the in vitro lines used to induce the tumors contained only a single insert of viral sequences and did not produce either a full-size 100,000-dalton (100K) large T-antigen or free viral genomes, no differences in the above-mentioned properties were observed. By contrast, in vitro cell lines containing multiple inserts of viral sequences, a functional 100K large T-antigen, and free viral genome induced tumor cells which displayed a reduced number of inserts of viral sequences and which did not produce either a functional 100K large T-antigen or free viral genomes. All of the in vitro lines and their tumor cell derivatives expressed the polyoma virus 55K middle and 22K small T-antigen species. Possible mechanisms for the selection in vivo against cells containing a functional 100K large T-antigen and consequently free viral genomes are discussed. (Author abstract) (21 Refs)

27. HYBRIDIZATION OF A MOUSE T-CELL LYMPHOCYTE LINE (HB1) WITH A POLYOMA VIRUS-TRANSFORMED MOUSE FIBROBLAST LINE.

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Exp Cell Res; 134(2):445-456 1981

The establishment of permanent T-lymphocyte cell lines by transformation with DNA viruses has not yet been achieved. This paper reports the successful transfer of polyoma virus genome into T-lymphocyte cells by somatic hybridization. A T-lymphocyte clone, HB1, derived from (DBA/2J x AKR) spleen cells, isolated in vitro by cloning in semi-solid agar, was fused with a polyoma (Py) virus-transformed fibroblast (C3HPy, clone 1). The authenticity of the hybrid C3H/HB was established by chromosome and histocompatibility antigen studies. This initial population and the various clones retained T-lymphocyte characteristics such as morphological appearance, growth properties (suspension culture) and differentiation antigen (Thy 1-2). The hybrid cell line and the various clones presented all the characteristics of Py transformation. Namely, they carried the Py genome originating from the fibroblastic parent and maintained Py virus tumor-associated antigens (TSTA, TSSA and T antigens). In most respects, this hybrid population resembled the C3HPy/Cl1 parent and exhibited the same tumorigenicity. (Author abstract) (28 Refs)

28. PRODUCTION OF INFECTIOUS EPSTEIN-BARR VIRUS IN MOUSE LYMPHOCYTES.

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Nature; 293(5831):399-401 1981

Epstein-Barr virus (EBV) DNA replication and antigen expression were studied in CBA or A/Sn mouse lymphocytes rendered EBV-susceptible by virus receptor implantation. EBV-determined nuclear antigen (EBNA) and early and virus capsid antigens were demonstrated in receptor-implanted cells exposed to EBV strains P3HR-1 or B95-8. Although EBNA levels were low, viral DNA replication occurred in 0.3%-4.7% of the infected cells. Unlike human lymphocytes, the mouse lymphocytes could be infected by both EBV strains, and the infectibility was not limited to B lymphocytes. Moreover, infection was not followed by the outgrowth of permanently transformed lymphoid cells and suppression of the virus lytic cycle. Lytically infected mouse cells continued to release infectious virus that induced EBV antigens in target Raji and Lukes cells. (12 Refs)

29. EPSTEIN-BARR VIRUS STRAIN- AND GROUP-SPECIFIC ANTIGENIC DETERMINANTS DETECTED BY MONOCLONAL ANTIBODIES.

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Int J Cancer; 28(3):321-327 1981

In order to differentiate Epstein-Barr virus (EBV) strains by serological markers we prepared hybridomas producing monoclonal antibodies against polypeptides of the QIMR-WIL EBV strain. These monoclonal antibodies were screened by indirect immunofluorescence techniques. Immunoprecipitation, using EBV-positive monoclonal antibodies and the protein A method, of 125I-labeled polypeptides from purified QIMR-WIL EBV particles, revealed that a series of monoclonal anti-

bodies against the four main surface and envelope polypeptides precipitating p340, p340/p240, p140, and p80 were obtained. When 125I-labeled polypeptides from purified P3HR-1 and B95-8 EBV particles were immunoprecipitated, it could be demonstrated that several anti-p340 (QIMR-WIL) antibodies recognized strain-specific antigenic determinants, while anti-p340/p240 (QIMR-WIL) as well as anti-p140 (QIMR-WIL) antibody clones reacted with antigenic sites which are in common wither among B95-8 or in addition to P3HR-1 polypeptides, Thus, monoclonal antibodies now provide a serological basis for EBV typing. (Author abstract) (31 Refs)

30. THE DETECTION OF EPSTEIN-BARR VIRUS RECEPTORS UTILIZING RADIOLABELLED VIRUS.

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J Gen Virol; 54(part1):191-195 1981

Epstein-Barr virus (EBV) was labeled with 3H-thymidine and purified about 1000-f old from the culture medium by ultracentrifugation on 5 to 30% dextran gradients. The presence of the virus was monitored by radioactivity and Epstein-Barr virus-determined nuclear antigen (EBNA) induction in sensitive indicator cells (Ramos). Peaks for both activities occurred in the 17 to 18% dextran fractions. Unlabeled virus recovered in the peak fraction was labeled with 125I. Both thymidine and 125I-labeled purified virus bound quantitatively to receptor-positive Burkitt lymphoma-derived cell lines but not to EBV-receptor-negative T-lymphocyte-derived cell lines. Thymidine-labeled virus that was allowed to bind to Raji cells was present in the interior of briefly trypsinized cells after 3 hr incubation at 37 C. The results provide a convenient method for detecting the EBV receptor by radioactively labeled virus. (Author abstract) (15 Refs)

31. THE SPONTANEOUS AND INDUCED SYNTHESIS OF EPSTEIN-BARR VIRUS ANTIGENS IN RAJI CELLS IMMOBILIZED ON SURFACES COATED WITH ANTI-LYMPHOCYTE GLOBULIN.

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J Gen Virol; 54(part2):397-401 1981

Immobilization of Raji cells on surfaces coated with anti-lymphocyte globulin (ALG) at low densities lead to the synthesis of Epstein-Barr virus (EBV) early antigen (EA) in up to 5% of the cells. At higher cell densities the percentage of antigen-positive cells decreased and at confluency no antigen synthesis was observed. Addition of iododeoxyuridine (IdUrd) to low density cultures increased the expression of EA to 20%, whereas in confluent cultures the cells could not be induced to synthesize EA. Treatment of cells in suspension with ALG failed to induce EA synthesis and did not potentiate the effect of IdUrd. Immobilized Raji cells proved to be suitable targets for superinfection with EBV derived from P3HR1 cultures. (Author abstract) (11 Refs)

32. CHARACTERISTICS OF EPSTEIN-BARR VIRUS ACTIVATION OF HUMAN B LYMPHOCYTES.

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J Exp Med; 154(3):832-839 1981

The correlation between the induction of viral antigens, de novo synthesis of cellular DNA, and immunoglobulin (Ig) secretion of in vitro Epstein-Barr virus (EBV)-infected B lymphocytes was studied. The induction of IgM-secreting cells and of DNA synthesis fell linearly as a function of B95-8 EBV dilution for highly purified B cells incubated with B95-8 EBV. The role of de novo DNA synthesis and transformation in the EBV-dependent induction of Ig secretion was studied. In comparing the EBV responsiveness of purified (B) vs nonpurified (B plus T lymphocytes), the kinetics of response was measured by the development of IgM-secreting cells. T cell-derived preparations showed a continuous increase of cells produci ng IgM, as well as a high proportion of Epstein-Barr nuclear antigen (EBNA)-positive cells as late as 14 days after initiating the culture, at a time when cell mixtures containing T cells showed very few Ig-secreting cells, as well as a low content of EBNA-positive cells. The results indicated that the EBV-induced activation of human B lymphocytes is a dose-dependent, one-hit phenomenon, and that the maturational step involved in the process of activation requires de novo DNA synthesis. (21 Refs)

33. SEQUENTIAL PRODUCTION OF IFN-ALPHA AND IMMUNE-SPECIFIC INF-GAMMA BY HUMAN MONONUCLEAR LEUKOCYTES EXPOSED TO HERPES SIMPLEX VIRUS.

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J Immunol; 127(3):1192-1196 1981

Both viral-induced interferon (IFN-alpha) and immune interferon (IFN-gamma) were produced in cultures of human peripheral mononuclear leukocytes (PML) exposed to UV light-inactivated herpes simplex virus (HSV). Comparable IFN titers (100 to 300 U) were present in supernatant media from PML of HSV-seropositive and -seronegative donors maintained for 2 days in culture. This 'early' IFN was not immunologically specific and had the characteristics of IFN-alpha. In contrast, PML from 20 of 21 (95%) seropositive donors, but only 2 of 22 (9%) seronegative subjects, produced IFN in day-5 cultures that had been washed on day 2 followed by the addition of fresh media without UV-HSV (p less than 0.0001). In addition, the geometric mean IFN titer of 35 U present in media from day 5 cultures of seropositive donors was significantly higher (p less than 0.0001) than those from seronegative subjects (less than 10 IFN U). This 'late' IFN was defined as immunologically specific by virtue of its being present almost exclusively in PML cultures from seropositive donors. Late-appearing, HSV-induced, immunospecific IFN-gamma had antigenic characteristics of both viral-induced IFN-alpha and mitogen-induced IFN-gamma. A considerable degree of overlapping sensitivity to anti-IFN-alpha and anti-IFN-gamma antibody existed in late IFN, but was not seen in standard, control specimens. The latter finding suggests that the possible existence of an IFN of antigenic character intermediate to IFN-alpha and IFN-gamma. Late IFN was not induced in PML cultures by UV-inactivated Newcastle disease virus (NDV). NDV did, however, induce high titers of early IFN-alpha in PML cultures of both HSV-seropositive and HSV-seronegative donors. HSV-stimulated lymphocyte blastic transformation occurred only in cultures of seropositive individuals, whereas none occurred in response to NDV. Delayed appearance of antiviral activity with the characteristics of IFN-gamma in HSV-stimulated PML cultures is a sensitive and specific measure of the human immune IFN response. Sequential synthesis of IFN-alpha and IFN-gamma in individual PML cultures provides an opportunity to examine regulation of IFN production in response to

virus with intrinsic IFN-inducing properties. (Author abstract) (22 Refs)

34. INHIBITION OF ADENOVIRUS-TRANSFORMED CELL ONCOGENICITY BY ADENO-ASSOCIATED VIRUS.

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Virology; 113(2):521-533 1981

Adeno-associated virus (AAV) has been shown to inhibit the oncogenicity and transforming ability of adenovirus (Ad). Using the H14b Ad-transformed hamster cell line, we have developed a model system in which to characterize the molecular events responsible for these inhibitory effects. AAV infection of H14b cells decreases their oncogenicity by approx threefold. The tumors that do arise are significantly smaller and have a longer latent period. AAV infection also alters the in vitro properties of the H14b cells, reducing cloning efficiency in methyl cellulose by 38-92% and saturation density by two- to four-fold. The molecular basis of this inhibition appears to be an inhibition of production of the 58K tumor antigen as determined by fluorescent antibody and immunoprecipitation studies. The reduction in the levels of tumor antigens are not due to alterations or loss of the Ad genome within H14b cells but may reflect an alteration in transcription or processing of Ad-specific mRNA. AAV infection of H14b cells does not lead to detectable levels of AAV DNA synthesis, but some AAV transcripts are made. This is the first instance in which AAV transcription has been detected in an Ad-transformed cell line. (Author abstract) (42 Refs)

35. UNINTEGRATED VIRAL DNA SEQUENCES IN A HAMSTER TUMOR INDUCED BY BOVINE PAPILLOMA VIRUS.

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J Virol; 39(3):945-949 1981

A fibrosarcoma was induced in a hamster by bovine papilloma virus Type 2 (BPV2). The content of BPV2 DNA sequences was measured by DNA-DNA and cRNA-DNA hybridizations. The tumor contained approx 300 BPV2 genome equivalents per cell. Southern blot hybridization indicated that the viral DNA was in free form, the entire genome most likely being present. In situ hybridization with BPV2 cRNA showed that multiple genome copies were present in each cell. Neither virus particles nor virus coat antigens could be detected in the tumor. A cell line was established from the fibrosarcoma, and the cells contained multiple copies of the BPV2 genome. The latter was in free form, and all of the DNA sequences appeared to be present in multiple copies and in all cells. An extensive search failed to reveal the presence of virus or viral antigens. (Author abstract) (29 Refs)

36. NATURAL OCCURRENCE OF DELETION MUTANT OF HUMAN PAPOVAVIRUS BK CAPABLE OF INDUCING T ANTIGEN.

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J Gen Virol; 54(part2):431-435 1981

Human papovavirus BK DNA resistant to digestion with EcoRI endonuclease had the capacity to direct synthesis of T antigen in human embryonic kidney cells. The study demonstrated the natural occurrence of defective deletion mutants with intact early functions of the viral genome. (Author abstract) (17 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

37. METASTATIC TUMOR CELL VARIANTS WITH INCREASED RESISTANCE TO INFECTION BY SEMLIKI FOREST VIRUS.

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J Immunol; 127(3):951-954 1981

Semliki Forest virus (SFV) is an interesting virus for cell interaction studies because it binds directly to the cells' major histocompatibility antigens. We used this reagent to study the expression and functional properties of H-2 molecules on murine tumor lines that are closely related but differ greatly in metastatic capacity. Tumor cell variants with high metastatic capacity showed an increased resistance to virus infection, an effect that was selective for SFV. Although the high metastatic tumor lines did not express less H-2 antigens than the low metastatic ones, they bound much less of the SFV viral glycoproteins. (Author abstract) (13 Refs)

38. G(ERLD): A CELL SURFACE ANTIGEN OF THE MOUSE RELATED TO XENOTROPIC MULV DEFINED BY NATURALLY OCCURRING ANTIBODY AND MONOCLONAL ANTIBODY. RELATION GIX, G(RADA1), G(AKSL2) SYSTEMS OF MULV-RELATED ANTIGENS.

Obata Y, Stockert E, DeLeo AB, O'Donnell PV, Snyder HW, Old LJ
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Exp Med; 154(3):659-675 1981

G(ERLD), one of the gp70-related cell surface antigens of murine leukemia virus (MuLV), is described and its features compared with the characteristics of other gp-70-related cell surface antigens, GIX, G(RADA1), and G(AKSL2). Sera from hybrid mice of crosses between B6 and 129, and their GIX congenic partners, B6-GIX+ and 129-GIX-, were tested for naturally occuring cytotoxic antibodies against a panel of transplanted tumor lines. Some sera were found to have high cytotoxic activity against ERLD, an x-ray-induced leukemia of B6 origin, as well as against other tumors. The G(ERLD) specificity was identified. The strain distribution of G(ERLD) was distinct from any known cell surface antigens. Quantitative differences in G(ERLD) expression characterized G(ERLD)+ strains. Most GIX+ strains were G(ERLD)+, while most GIX- negative strains were G(ERLD)-. Hybrids between G(ERLD)+ and G(ERLD)- strains expressed approx half the quantity of G(ERLD) found in the G(ERLD)+ parent. G(ERLD) was expressed in G(ERLD)+ mouse strains and in some G(ERLD)- strains. G(ERLD) could be expressed on tumor cells in the absence of other MuLV antigens. The occurrence of natural antibody with high ERLD reactivity was restricted to B6, B6-GIX+, C57L, and hybrid mice of crosses between B6, 129, and GIX congenic partner strains. Experimental results suggested that G(ERLD) expression was controlled by a single locus in B6, by two unlinked loci in 129 and by three unlinked loci in B6-GIX+ mice. It was suggested that one of the loci in 129 and B6-GIX+ mice may be identical or closely linked to the locus controlling GIX antigen expression.

Evidence suggested that G(ERLD) is a determinant associated with xenotropic and dualtropic MuLV gp70 molecules, but that it is unstable and tends to be lost during standard purification procedures. A monoclonal antibody to G(ERLD) was produced. (37 Refs)

39. NEW CELL SURFACE GP70 RELATED TO FRIEND MINK CELL FOCUS-INDUCING VIRUS IS EXPRESSED ON FRIEND VIRUS-INDUCED ERYTHROLEUKEMIC SPLEEN CELLS AFTER ELIMINATION OF ECOTROPIC FRIEND VIRUS GP70 IN RFV-3R/S MICE.

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J Exp Med; 154(3):868-882 1981

The expression of individual Friend virus (FV)-encoded proteins in FV leukemic spleen cells was studied at various times in the course of FV leukemia in order to determine the role of anti-FV antibody in altering the expression of viral antigens and infectious virus release in these cells. The results indicated that the presence of anti-FV antibody late in the disease is associated with a decreased expression of Friend helper virus (FMuLV)-encoded intracellular and cell surface proteins, whereas the expression of the replication-defective spleen focus-forming virus (SFFV)-encoded proteins appears to be minimally altered. This selective loss of F-MuLV proteins appeared to correlate with the specificity of the mouse anti-FV antibody that was found to recognize F-MuLV but not SFFV-specific proteins. In addition, a new gp70 molecule was identified on the surface of FV leukemic spleen cells late in the disease. This molecule differed from gp70 in the ecotropic Friend virus, which was inoculated into these mice, in that it shares cross-reactivity with Friend mink cell focus-inducing virus. The potential importance of this recombinant is discussed. (32 Refs)

40. ESTIMATION OF MOUSE MAMMARY TUMOR VIRUS GP52 ABUNDANCE BY PROTEIN A ASSAY: A COMPARISON OF VIRAL ANTIGEN EXPRESSION ON C3H AND GR MAMMARY TUMOR CELLS.

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Intervirology; 15(2):111-120 1981

An adherent cell isotopic staphylococcal protein A test (ISPAT) was used to estimate the abundance of mouse mammary tumor virus (MMTV) gp52 cell surface antigen (CSA) on mammary tumor cells. Protein A assays were first utilized, not strictly as a means of antigen detection, but as a means to determine the kinetics of dexamethasone-mediated changes in gp52 cell surface expression. Results indicated increases in gp52 CSA within 4 hr of dexamethasone treatment and max levels of antigen expression within 12-24 hr after treatment. Comparison of gp52 determinants on dexamethasone-stimulated mammary tumor cells demonstrated a greater abundance on C3H Mm5mt/cl than on GR-MMTV cultures. Parallel antigen assays with gp52 and Rauscher murine leukemia virus (R-MuLV) antisera demonstrated that GR-MMTV cells expressed fewer C-type determinants and thus a more preferential expression of gp52 determinants than other cell lines tested. The gp52/R-MuLV binding ratio was only 2.4:1 for C3H cultures in contrast to 5.7:1 for GR cultures. In addition, a comparison of gp52 expression on viral producer and nonproducer cells provided a quantitative estimate of the extent of expression which occurred in a retrovirus nonproducer culture. Results of ISPAT demonstrated that 75% of the gp52 detected on producer cells was present on nonproducer cultures. Comparison of the expression of gp52 CSA and the release of gp52 into culture fluids during hormone treatments demonstrated that both assays (ISPAT and gp52 radioimmunoassay) detect and quantitate coordinate changes in the expression and release of MMTV gp52. In antibody excess, protein A assays provided quantitative estimates of CSA abundance not offered by alternative methods of CSA detection. (Author abstract) (17 Refs)

41. CHARACTERIZATION OF SARCOMA-POSITIVE, LEUKEMIA-NEGATIVE (S+L-) HUMAN CELLS INDUCED BY THE FELINE LEUKEMIA VIRUS PSEUDOTYPE OF MOLONEY SARCOMA VIRUS.

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Proc Soc Exp Biol Med; 167(4):597-606 1981

The isolation and characterization of sarcoma-positive, leukemia-negative (S+L-) human cells induced by the feline leukemia virus pseudotype of Moloney sarcoma virus (Mo-MSV(FeLV)) is reported. The four clones selected for study were negative for infectious virus and type C virus particles, but, contained a rescuable MSV genome and murine leukemia virus (MuLV)-specific antigen, such as the gag gene products, p15, p12, and p30, and lacked the env gene protein (gp 70). The cells were all tumorigenic in nude mice. In human, NRK, and NIH 3T3 mouse embryo cells, the Mo-MSV rescued by baboon type C virus (M-7), Mo-MSV(M-7), readily produced foci. Human cells transformed by MoMSV(M-7) were virus producers, while Mo-MSV(M -7)-transformed NRK and NIH 3T3 mouse embryo cells were S+L- cells. These latter cells were negative for infectious virus but contained a rescuable MSV genome and MuLV antigen. (21 Refs)

42. GENERATION OF TRANSFORMING VIRUSES IN CULTURES OF CHICKEN FIBROBLASTS INFECTED WITH AN AVIAN LEUKOSIS VIRUS.

Stavnezer E, Gerhard DS, Binari RC, Balazs I
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J Virol; 39(3):920-934 1981

During serial passages of an avian leukosis virus (the transformation-defective, src deletion mutant of Bratislava 77 avian sarcoma virus, designated tdB77) in chicken embryo fibroblasts, viruses which transformed chicken embryo fibroblasts in vitro emerged. Chicken embryo fibroblasts infected with these viruses (SK770 and SK780) had a distinctive morphology, formed foci in monolayer cultures, and grew independent of anchorage in semisolid agar. Bone marrow cells were not transformed by these viruses. Another virus (SK790) with similar properties emerged during serial subcultures of chicken embryo fibroblasts after a single infection with tdB77. The 50S to 70S RNAs isolated from these viruses contained a tdB77-sized genome (7.6 kilobases), 8.7-and 5.7-kilobase RNAs, and either a 4.1-kilobase RNA or a 4.6-kilobase RNA. These RNAs did not hybridize with cDNA's representing the src, erb, mac, and myb genes of avian acute transforming viruses. Cells transformed by any one of the SK viruses (SK770, SK780, or SK790) synthesized two novel gag-related polyproteins having mol wt of 110,000 (p110) and 125,000 (p125). We investigated the compositions of these proteins with monospecific antiviral protein sera. We found that p110 was a gag-pol fusion protein which contained antigenic determinants of p19, p27, and re-

verse transcriptase and that p125 contained only gag determinants, leaving 49,000 daltons which was antigenically unrelated to the structural and replicative proteins of avian leukosis viruses. An analysis of the SK viral RNAs with specific DNA probes indicated that the 5.7-kilobase RNA contained gag sequences but lacked pol sequences and, therefore, probably encoded p125. The transforming ability, the deleted genome, and the induced polyproteins of the SK viruses were reminiscent of the properties of several replication-defective acute transforming viruses. (Author abstract) (51 Refs)

43. CORRELATION OF BLOOD LYMPHOCYTE NUCLEAR POCKET PREVALENCE WITH ENZOOTIC BOVINE LEUKEMIA P24 VIRAL ANTIBODY TITERS.

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Am J Vet Res; 42(8):1395-1399 1981

The quantitative relationship between radioimmunoassay serotiters to p24 enzootic bovine leukemia viral antigen and the prevalence of lymphocytic nuclear pockets (LNP) was studied in 5 54 clinically normal dairy cows and bulls. Of the animals, 69% were seronegative. Of the seronegative animals, 44% had no observed LNP, whereas 93% of the seronegative animals had less than 1% LNP. However, 2.3% of the seronegative animals had substantially increased (greater than 2%) numbers of LNP, and conversely, 24% of the seropositive animals had no observed LNP. Statistical evaluation of the data, using contingency table and regression methods, provide significant (p less than 0.0001) evidence for a positive association between LNP prevalence and p24 bovine leukemia viral serotiters. Although significant, the association was weak, and hence LNP number had little value for predicting serotiter. (Author abstract) (23 Refs)

44. CLEAVAGE OF RAUSCHER LEUKAEMIA VIRUS (R-MULV) PR65GAG BY THE MOLONEY LEUKAEMIA . VIRUS (M-MULV) PROTEOLYTIC ACTIVITY PRODUCES THE R-MULV-SPECIFIC BUT NOT THE M-MULV-SPECIFIC 40,000 DALTON INTERMEDIATE POLYPEPTIDE.

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Dept. Microbiology, Mie Univ. Sch. Medicine, 174 Edobashi-2-Chome, Tsu, Mie, Japan 514
J Gen Virol; 54(part1):33-38 1981

The discovery of a 1,500 dalton mol wt difference in Moloney leukemia virus (M-MuLV) and Rauscher leukemia virus (R-MuLV) intermediate products was used to monitor the results of in vitro cleavage of R-MuLV cpre precursor polyprotein Pr65gag by the proteolytic activity present in M-MuLV extracts. Analysis by sodium dodecyl sulfate-polyacrylamide gel electrophoresis showed that cleavage yields an MuLV Pr40gag polypeptide; at no point during the reaction with increasing amounts of the M-MuLV extract containing the proteolytic activity was any material found in a band position corresponding to the M-MuLV protein of 1,500 dalton higher mol wt, named Pr41.5gag. The possibility of a rapid cleavage of R-MuLV Pr65gag to MuLV Pr41.5gag, then to its antigenic determinant p30, was ruled out by cleaving 35S-methionine-R-MuLV Pr65gag with the unlabeled M-MuLV extract. Only labeled MuLV Pr40gag and no labeled MuLV Pr41.5gag was found. A subspecies difference in size between M-MuLV Pr41.5gag and R-MuLV Pr40gag is apparent; if M-MuLV extracts contain only one Pr65gag protease, the fact that M-MuLV extract proteolytic activity cleaves R-MuLV Pr65gag to R-MuLV Pr40gag and not to M-MuLV Pr41.5gag suggests that the specificity for initial cleavage is built into the corresponding Pr65gag precursors and not into the corresponding proteolytic factors which supply the activity. (11 Refs)

45. PHYSICOCHEMICAL AND IMMUNOLOGICAL PROPERTIES OF TISSUE DNA FROM MICE WITH ONCORNAVIRUS-INDUCED LEUKEMIA.

Chamova KG, Perelaznyi AA, Guseva NI
Res. Lab. Experimental Immunobiology, Moscow, USSR
Biull Eksp Biol Med; 91(7):60-62 1981

DNA specimens isolated from the spleen of mice with leukemia induced by Freund leukemia virus or by Rauscher virus were found to contain the antigenic determinants that were absent in the normal homologous DNA. Denaturation of leukemic DNA did not affect its immunologic specificity. (10 Refs) (In RUS)

46. RELATIVE EFFICIENCY OF TEST PROCEDURES TO DETECT LYMPHOID LEUKOSIS VIRUS INFECTION.

Fadly AM, Okazaki W, Smith EJ, Crittenden LB
Science and Education Admin., Agricultural Res., US Dept. Agriculture, Regional Poultry Res. Lab., 3606 East Mount Hope Road, East Lansing, MI, 48823
Poult Sci; 60(9):2037-2044 1981

The efficacy of test procedures in the detection of avian lymphoid leukosis virus (LLV) or antigen in various test materials collected from day-old chicks and adult hens was compared. When blood and meconium collected from 297 chicks were assayed for LLV by the phenotypic mixing (PM) test, blood was found to be superior to meconium in identifying newly hatched LLV-infected chicks. When albumin samples from freshly laid eggs were assayed for virus and LLV-group-specific (gs) antigen, 100% concordance was observed for both the PM and direct complement fixation (D-CF) tests. The enzyme-linked immunosorbent assay was found to be more sensitive than the D-CF test in the detection of LLV and GS antigen in the albumin of eggs. A high percentage of agreement was observed when PM and D-CF were used on blood, cloacal swab, and albumin samples collected from adult hens. All hens that were identified as LLV-positive at 28 and 48 wk were also so identified at 19 wk of age. Discrepancies between results obtained with different test procedures were clear. When cloacal swabs and albumin were taken from hens that are producing endogenous virus or those that are producing gs antigen and chick helper factor, but lack complete virus, were tested for gs antigen by the D-CF test, 7/12 of the swabs collected from chickens with endogenous virus were positive for gs antigen. Large amounts of endogenous virus or gs antigen were present in the swabs, but only 1/48 albumin samples were positive. (21 Refs)

47. WILD MOUSE ECOTROPIC MURINE LEUKEMIA VIRUS INFECTION OF INBRED MICE: DUAL-TROPIC VIRUS EXPRESSION PRECEDES THE ONSET OF PARALYSIS AND LYMPHOMA.

Hoffman PM, Davidson WF, Ruscetti SK, Chused TM, Morse HC
Veterans Admin. Medical Center, Dept. Neurology, Basic and Clinical Immunology and Microbiology, Medical Univ. South Carolina, Charleston, SC, 29545
J Virol; 39(2):597-602 1981

NFS/N mice inoculated at birth with an ecotropic murine leukemia virus (Cas-Br-M MuLV) obtained from wild mice developed hind limb paralysis beginning at 7 wk of age and

nonthymic lymphomas beginning at more than 20 wk of age. Studies of 1-to 7-wk-old Cas-Br-M MuLV-infected mice showed the following: (i) a marked increase in nonecotropic MuLV-related antigens on spleen cells but not thymocytes beginning at 2 wk; (ii) the appearance of dual-tropic mink cell focus-forming (MCF) MuLV-related gp70 in spleen but not thymus or brain cells at 4 wk; and (iii) the isolation of infectious MCF MuLV from spleen cells of 7-wk-old mice. A role for MCF MuLV in Cas-Br-M MuLV-induced nonthymic lymphomas is indicated by these studies, and a role for recombinant MuLV in neurological disease is considered. (Author abstract) (22 Refs)

48. ESTABLISHMENT AND PROPAGATION OF A BOVINE LEUKAEMIA VIRUS-PRODUCING CELL LINE DERIVED FROM THE LEUKOCYTES OF A LEUKEMIC COW.

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J Gen Virol; 54(part2):357-365 1981

A cell line (LB59Ly) derived from the WBC of a leukemic cow was established as a monolayer, which spontaneously released large amounts of a retrovirus. This virus was found to be indistinguishable from the bovine leukemia virus (BLV) produced by the commonly used high-producing heterologous cell line (FLK-BLV). Like the latter, its reverse transcriptase activity was greater in the presence of Mg++ cations than in the presence of Mn++ cations; its polyacrylamide gel electrophoresis pattern showed the presence of gp51, p24, p15, p12 and p10, and the antigenicity of the two major proteins completely cross-reacted with those of BLV from FLK-BLV cells. the virus was infectious and induced early and late polykaryocytosis, the specificity of which was demonstrated by use of specific anti-BLV sera. (Author abstract) (26 Refs)

49. IN VITRO PROTEOLYTIC CLEAVAGE OF GAZDAR MURINE SARCOMA VIRUS P65GAG.

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Dept. Tumor Virology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
J Virol; 39(3):963-967 1981

Moloney murine leukemia virus, disrupted in concentrations of 0.1 to 0.5% Nonidet P-40, catalyzed the cleavage of p65, the gag gene polyprotein of the Gazdar strain of murine sarcoma virus, into polypeptides with sizes and antigenic determinants of murine leukemia virus-specified p30, p15, pp12, and p10. Cleavage performed in the presence of 0.15% Nonidet P-40 in water yielded polypeptides of approx 40,000 (P40) and 25,000 (P25) Mr. In vitro cleavage performed in a buffered soln containing dithiothreitol in addition to 0.1% Nonidet P-40 allowed the efficient processing of P40 to p30 and a band migrating with p10. Immunoprecipitation with monospecific sera indicated that P40 contained p30 and p10, whereas P25 contained p15 and pp12 determinants. P40 and P25 are similar in size and antigenic properties to Pr40gag and Pr25gag observed in infected cells. (Author abstract) (16 Refs)

50. CURING OF VIRUS PERSISTENT INFECTION IN HVJ (SENDAI VIRUS) CARRIER HAMSTER TUMOR CELLS BY TRANSPLANTATION.

Ogura H, Sato H, Hatano M
Dept. Virology, Cancer Res. Inst., Kanazawa Univ., 13-1, Takaramachi, Kanazawa 920, Japan
Gan; 72(4):498-503 1981

Transplantability of hamster tumor cells in the syngeneic system was considerably reduced by HVJ (Sendai virus) persistent infection of the cells, but these HVJ carrier cells still showed tumorigenicity, especially at high transplantation doses. Therefore, the existence of HVJ antigens or infectious HVJ in the tumors formed in vivo by transplanted HVJpi (temperature-sensitive HVJ) or HVJo (non-temperature-sensitive HVJ) carrier tumor cells was examined in relation to the reduced transplantability of the cells. In stamp preparations of tumor cells, no HVJ antigens were detected from 14 days after transplantation, though they were positive if observed within 7 days. Infectious HVJ particles could also be recovered from tumor tissues which were cocultivated with LLCMK2 cells within 7 days after transplantation. However, tumor cells recultured in vitro after more than 3 wk post transplantation did not show HVJ antigens, even after various attempts at HVJ induction such as culture at low temperature, serial passages in vitro, treatment with 5-iododeoxyuridine, etc. The cytopathic effects and fluorescent antibody staining of these cells became positive when they were superinfected with wild-type HVJ, indicating a new establishment of HVJ infection after the curing of the HVJ genome initially carried. In contrast, the original HVJ carrier tumor cells were demonstrated to be completely resistant to this superinfection (one of the characteristics of persistent infection). These results seem to show that HVJ persistence in its carrier tumor cells was ultimately cured by transplantation and may provide at least a partial explanation of why the xenogenization of tumor cells by HVJ persistent infection was relatively weak. (Author abstract) (12 Refs)

51. IN VITRO CURING OF PERSISTENT INFECTION OF HVJ (SENDAI VIRUS) CARRIER TUMOR CELLS BY SPLEEN CELLS.

Ogura H, Sato H, Hatano M
Dept. Virology, Cancer Res. Inst., Kanazawa Univ., 13-1, Takaramachi, Kanazawa 920, Japan
Gan; 72(4):504-511 1981

The viral antigens of hamster tumor cells persistently infected with HVJ (Sendai virus) disappeared upon transplantation, showing that HVJ persistent infection can be cured in vivo. In order to analyze these phenomena, an attempt to achieve a similar cure in vitro was made. When HVJ carrier tumor cells (GM2-HVJpi) were cultured in the presence of sera from GM2-HVJpi-tumor-bearing hamsters or rabbit antiserum against glycoproteins (GP) of HVJ, the cells showed only weak stainability with fluorescent antibody (FA). Lymphokines produced by spleen cells from GM2-HVJpi-tumor bearers could not cause GM2-HVJpi cells to lose their viral antigens. However, the viral antigens of GM2-HVJpi cells became unde tectable upon cocultivation with spleen cells from either normal or GM2-HVJpi-tumor-bearing hamsters. These cells from which HVJ antigens had been lost were reconfirmed to be cured in vitro through single colony isolation and subsequent establishment of a new HVJ infection after superinfection of the isolated cells with HVJ. The above results indicate that the curing of virus persistent infection in HVJ carrier tumor cells by transplantation was due to the in vivo action of

spleen cells against transplanted HVJ carrier tumor cells. (Author abstract) (17 Refs)

52. QUANTITATION OF VIRAL ANTIGENS RELEASED INTO PLASMA AND CULTURE FLUIDS BY MURINE MAMMARY TUMOR CELLS.

Ritzi EM, Smith BA, Stolfi RL, Martin DS
Univ. Tennessee Center for Health Sciences, Memphis, TN, 38163
Cancer Res; 41(10):3885-3890 1981

Radioimmunoassays capable of measuring mouse mammary tumor virus (MMTV) mol wt 52,000 envelope glycoproteins (gp52) and mol wt 27,000 proteins (p27) have been used to quantitatively compare plasma concentrations of these viral antigens in mice bearing spontaneous mammary tumors. Although gp52 was detected in the plasma of all tumor-bearing mice tested, p27 was detected in only a portion of tumor-bearing animals. In p27-positive animals, gp52 was detected in higher concentrations than p27. These findings demonstrate that gp52 has preferential utility as a plasma marker for the presence of mammary tumors in MMTV-infected hybrid (BALB/c x DBA/8 F1), Paris RIII, and C3H/HeJ mice. In addition, cultures of MMTV-producing cells [GR-MMTV and MMTV(C3H)Fe1] were used as models to study the release of viral antigens in the absence of serum antibody or additional host factors. Comparisons of extracellular soluble and particulate antigen concentrations demonstrated that gp52 and p27 were present in substantially higher concentrations as soluble than virion-associated antigens. The mean ratio of non-virion-associated gp52 to virion-associated gp52 was 12:5:1 for GR-MMTV cells and 37:3:1 for MMTV(C3H)Fe1 cells. The marked stability of MMTV in culture fluids suggested that virion breakdown was not responsible for the accumulation of soluble viral antigens in culture. The information obtained suggests that abundant virus-free antigens may be of greater use than virion-associated antigens as a source of viral antigen to evaluate mammary tumor status. (Author abstract) (20 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

53. CYTOTOXIC CELLS INDUCED IN VITRO BY EPSTEIN-BARR VIRUS ANTIGENS.

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Dept. Bacteriology and Immunology, Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Cell Immunol; 63(1):91-105 1981

Lymphocyte blastogenesis and cytotoxicity for lymphoid cells line (LCL) were induced in cells from immune donors by stimulation in vitro with irradiated Epstein-Barr Virus (EBV). Velocit y sedimentation of blastogenic populations indicated that much of the killing was associated with large E-rosetting cells; it was reduced by [3H]thymidine suicide immediately prior to sedimentation. Target cells were killed irrespective of EBV content or sensitivity to natural killer (NK cells), though the pattern of lysis varied with repeated use of individual donors. Up to 9% of the normal resting lymphocytes became blastogenic though fewer than 30% of the dividing cells at termination of culture had undergone more than one division. It is suggested that EBV antigens induce a polyclonal activation of cytotoxic T cells. The possible significance of this response is discussed with particular reference to the origin of non-EBV-specific cytotoxic blast cells in infectious mononucleosis. (Author abstract) (46 Refs)

54. IMMUNITY TO VARICELLA-ZOSTER VIRUS IN CHILDREN WITH ACUTE LEUKEMIA OR OTHER MALIGNANCIES. PART 1. LYMPHOCYTE BLASTOGENIC RESPONSE TO VARICELLA-ZOSTER VIRUS ANTIGEN IN CHILDREN WITH ACUTE LEUKEMIA.

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Dept. Pediatrics, Mie Univ., Tsu, Mie 514, Japan
Shonika Kiyo; 27(1):40-41 1981

Lymphocyte blastogenic response to Varicella-Zoster virus antigen was studied in 78 adults or children, including 11 children with acute lymphocytic leukemia (ALL) who had had varicella and 13 vaccinated children with ALL. Stimulation index values of healthy children and adults who had had varicella and of leukemic children who had had varicella or had been vaccinated were statistically higher than those children who had not been previously infected. Results indicated that lymphocytes of leukemic children in remission can respond normally to Varicella-Zoster virus antigens. (no Refs)

55. IMMUNOTHERAPY OF MURINE LEUKEMIA. V. PROTECTION AGAINST FRIEND LEUKEMIA VIRUS-INDUCED IMMUNE COMPLEX GLOMERULONEPHRITIS BY PASSIVE SERUM THERAPY.

Sanfilippo F, Genovesi EV, Collins JJ
Duke Univ. Medical Center, P.O. Box 3712, Durham, NC, 27710
JNCI; 67(3):703-717 1981

The development of immune complex glomerulonephritis in DBA/2 mice infected with Friend murine leukemia virus (F-MuLV) was compared with that in mice protected against virus-induced disease by administration of chimpanzee anti-F-MuLV antiserum (CaF-MuLV). Morphologic analysis of glomeruli from viremic (infected) normal chimpanzee serum-treated animals revealed significant renal disease within 2 wk following virus inoculation, with glomerular immune complex deposits and C-type viral particles seen by electron microscopy. Localization of F-MuLV envelope and core antigens (gp71 and p30, respectively) was also detected by immunofluorescence, as was murine IgG and C3. However, age-matched DBA/2 mice treated with CaF-MuLV antiserum alone or following F-MuLV inoculation showed no evidence of systemic disease and neither localizati on of F-MuLV antigens nor detectable virus particles. These data indicate that in addition to erythroleukemia, F-MuLV infection results in severe immune complex glomerulonephritis and that passive immunotherapy can protect susceptible mice from both aspects of viral pathogenesis. (Author abstract) (30 Refs)

56. SPECIFICITIES OF KILLING BY T LYMPHOCYTES GENERATED AGAINST SYNGENEIC SV40 TRANSFORMANTS: CROSS-REACTIVITY OF THE H-2KBM1 THROUGH KBM4 H-2 MUTANT ALLELES IN KB-RESTRICTED SV40-SPECIFIC KILLING.

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J Immunol; 127(3):1207-1211 1981

SV40-specific cytotoxic T lymphocytes (CTL) produced in H-2Kb recombinant mice do not kill SV40-transformed mouse embryo fibroblast (MEF) targets from strains bearing the histocompatibility mutations H-2Kbm1, Kbm2, Kbm3, and Kbm4

although CTL from SV40-immune H-2db-bearing recombinant mice kill all of the SV40-transformed mutant cell lines with similar kinetics. Similarly, B6.C-H-2bm1, B6.C-H-2bm2, B6-H-2bm3, and B6.C-H-2bm4 spleen cells immunized with syngeneic SV40-transformed cell lines do not kill recombinant transformed cell lines bearing H-2Kb antigens whereas the same immune cell populations will kill H-2Db-bearing recombinant targets with similar dose-response relationships. Although SV40-transformed cell lines do not cross-react with H-2Kb-bearing targets as restriction elements for SV40-specific CTL, allogeneic Kb-specific CTL displayed significant killing of all mutant cell lines, as did allogeneic Db-specific CTL. Apparently, the functional cross-reactivity of H-2Kb-encoded molecules as restriction elements for SV40-specific T cell-mediated immunity is effectively abolished by the bm1 through bm4 series of mutations at H-2Kb while a significant proportion of the determinants recognized by allogeneic Kb-specific immune CTL are left unmodified. Two possible explantations could account for these findings. Either (1) the mutations have altered the ability of Kb-encoded cell surface elements to form an immunogenic complex with SV40-specific cell surface antigens and the mutant cell lines neither generate K-end-restricted populations of CTL nor do they serve as targets for K-end-restricted killing; or (2) H-2Kb mutant antigens form immunogenic complexes with SV40 antigens but the populations of CTL generated by syngeneic SV40 immunization are so much more specific than alloimmune CTL (or fewer clones of CTL are activated in syngeneic immunity) that little or no cross-reactivity can be seen between these 4 H-2 mutations and the 'wild-type' H-2Kb restriction element. (Author abstract) (31 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

57. MECHANISM OF INHIBITION OF EPSTEIN-BARR VIRUS REPLICATION BY PHOSPHONOFORMIC ACI D.

Datta AK, Hood RE
Cancer Res. Center, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Virology; 114(1):52-59 1981

The trisodium salt of phosphonoformic acid (PFA) inhibits Epstein-Barr virus (EBV) replication in lymphoblastoid cells at concentrations nontoxic to cellular growth. The synthesis of early antigen (EA) in the infected cells is not affected by the drug under conditions when viral capsid antigen (VCA) and viral DNA synthesis are inhibited to the extent of 75 and 90%, respectively. In vitro studies with partially purified DNA polymerases show that PFA inhibits EBV-associated DNA polymerase to a greater extent than it inhibits alpha- and beta-polymerases. Enzyme kinetic analysis reveals a linear noncompetitive inhibition with four deoxytriphosphates and a typical uncompetitive inhibition with variable concentrations of DNA as substrate at saturating deoxytriphosphate concentrations. The apparent inhibition constant for EBV-associated polymerase was in the range of 2-3 uM. The inhibitory effect is exerted at the pyrophosphate binding site of DNA polymerase. Although productive viral DNA synthesis is completely arrested by the drug, the virus-associated DNA polymerase activity is expressed normally in superinfected Raji cells even in the presence of the drug. We propose that in addition to potential therapeutic value, the compound could be used as a tool to study some of the restricted early functions of virus in the absence of productive viral DNA synthesis. Induction of viral DNA polymerase can also be used as an additional marker for expression of early viral functions. (Author abstract) (36 Refs)

58. PROTECTIVITY OF HERPES SIMPLEX VIRUS ANTIGENS: STUDIES IN MICE ON THE ADJUVANT EFFECT OF PICLC AND ON THE DEPENDENCE OF PROTECTION ON T CELL COMPETENCE.

Hilfenhaus J, Christ H, Kohler R, Moser H, Kirchner H, Levy HB
Res. Lab. Behringwerke AG, D-3550 Marburg, W. Germany
Med Microbiol Immunol (Berl); 169(4):225-235 1981

Immunocompetent C57/6J Bom nu/+ mice and their T-cell-deficient nu/nu littermates were equally susceptible to primary herpes simplex virus type 1 (HSV-1) infections. The immunocompetent mice were protected against HSV-1 or type 2 (HSV-2) infections by preimmunization (2 wk before infection) with heat-inactivated whole virus or HSV-1 envelope antigen (HSV-1 EAG). Heat-inactivated HSV-2 was equally protective against HSV-1 and HSV-2 infections. Heat-inactivated HSV-1 was less protective against HSV-2 infections than against HSV-1 infections. The low immunizing capacity of HSV-1 EAG was greatly enhanced by using polyinosinic:polycytidylic acid complex with poly-L-lysine in carboxymethyl cellulose (PICLC) as an adjuvant. PICLC alone had no protective effect against HSV-1 infection. The immunoincompetent nu/nu mice were not protected against HSV-1 infection by preimmunization with HSV-1 EAG, even in PICLC adjuvant. It is concluded that T-cell competence is required for the establishment of a protective immunity against HSV infection by HSV-1 EAG preimmunization. (30 Refs)

59. ENHANCEMENT OF EPSTEIN-BARR VIRUS-INDUCED TRANSFORMATION OF HUMAN LYMPHOCYTES BY TELEOCIDIN.

Hoshino H, Miwa M, Fujiki H, Sugimura T, Yamamoto H, Katsuki T, Hinuma Y
Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan
Cancer Lett; 13(4):275-280 1981

The effect of teleocidin and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on Epstein-Barr virus (EBV)-induced transformation in human lymphocytes was examined. Human umbilical cord lymphocytes were infected with the B95-8 strain of EBV and cultured in soft agar. Teleocidin enhanced colony-forming efficiency approx 5x at 0.1 nanog/ml. TPA had a similar but lesser effect at the same concentration. Optimal concentrations were, respectively, 2.2 and 1.6 x 10(-10) M. Using the P3HR-1 EBV strain, which unlike strain B95-8 induces early antigen (EA) in C-6 lymphoblastoid cells after superinfection, the effects on plating efficiency were tested. The number of EA-positive cells as detected by immunofluorescence increased 2-3x in the presence of teleocidin or TPA. Cultures not infected with P3HR-1 produced less than 1% EA-positive cells even with teleocidin or TPA. Colony-forming efficiency of the newly transformed lymphoblastoid cells was 2x as great in the presence of 0.5 nanog/ml teleocidin as in its absence. TPA is known to have a similar effect. The evidence suggests that teleocidin and TPA act similarly to enhance the efficiency of EBV infection of cord blood lymphocytes and also to stimulate colony formation of lymphocytes newly transformed by EBV. (19 Refs)

OTHER RELATED STUDIES

60. ESCAPE OF METASTASIZING CLONAL TUMOR CELL VARIANTS FROM TUMOR-SPECIFIC CYTOLYTIC T LYMPHOCYTES.

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J Exp Med; 154(2):557-562 1981

The spontaneous, highly metastatic ESb tumor variant arose from the chemically-induced DBA/2 lymphoma L5178Y (Eb) tumor. It is characterized by a tumor-associated transplantation antigen (TATA). This antigen is recognized by syngeneic secondary antitumor cytolytic T lymphocytes (CTL). During metastasis of twice-cloned cell lines of this tumor, immunoresistant variants develop that are not susceptible to lysis by CTL. These variants are detected in the spleens of normal syngeneic mice. Experimental evidence indicates that ESb TATA is reduced or non-existent in the variants. They apparently did not have a differentiated TATA. The variants remained stable in over 100 tissue culture generations. They were shown not to b e preexisting in the original tumor cell population. The high frequency with which these variants occur is suggested as a cause of the ineffectiveness of specific immunization against the ESb tumor type. (15 Refs)

61. TUMOUR MARKERS: THEIR ROLE IN CLINICAL MEDICINE.

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Practitioner; 225(1356):839-841,843-844,846-849 1981

Biochemical tumor markers currently used in diagnosis and monitoring responses to treatment are human chorionic gonadotropin (HCG) in trophoblastic tumors; beta subunit HCG and alpha-fetoprotein (AFP) in testicular tumors; AFP (if the initial titer is very high) in hepatomas; acid phosphatase in prostatic cancer; catecholamines in neuroectodermal tumors; and calcitonin in medullary carcinoma of the thyroid. Carcinoembryonic antigen (CEA) assays are useful for monitoring responses to treatment in patients with colorectal cancer, but cannot be used in diagnosis. Certain lung tumors (especially oat cell carcinomas) secrete ectopic ACTH, antidiuretic hormone, and/or calcitonin. These ectopic hormones may also be present in patients with chronic obstructive pulmonary disease, but the ectopic hormones associated with lung cancer are often of abnormally high mol wt. Assays for these high-mol wt hormones may be useful for monitoring responses to therapy. Adenocarcinomas and squamous cell carcinomas of the lung may produce CEA, alkaline phosphatase, and gamma-glutamyl transpeptidase. However, elevated CEA levels are present in smokers and patients with many non-neoplastic and inflammatory diseases, and the enzymes are not tumor-specific. At present, the role of biochemical markers in the management of the common solid tumors is rather limited. The use of tumor markers in breast and lung cancer must await further research. Monoclonal antibody technology should soon provide satisfactory antibodies for immunolocalization and immunocytochemistry studies in breast cancer patients. (12 Refs)

62. HODGKIN'S DISEASE: ESTABLISHMENT AND CHARACTERIZATION OF FOUR IN VITRO CELL LINES.

Diehl V, Kirchner HH, Schaadt M, Fonatsch C, Stein H, Gerdes J, Boie C

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J Cancer Res Clin Oncol; 101(1):111-124 1981

Four in vitro cells established from the pleural effusions of two Hodgkin's disease (HD) patients and from the blood and bone marrow of a third were characterized morphologically, immunologically, and biochemically. The malignant nature of the cultured cells was confirmed by the presence of structural and numerical chromosome abnormalities, the monoclonality of marker chromosomes, and the lack of Epstein-Barr virus-specific antigens. The cells gave rise to tumors in nude mice following in tracranial transplantation and induced sc tumors when embedded on plasma dots before transplantation. All four lines were positive for Ia-like antigens, T-cell receptors, acid phosphatase, and acid esterase; they were negative for lysozyme peroxidase, chloracetate esterase, surface Ig or cytoplasmic Ig (CIg), and receptors for complement 3b, complement 3d, IgG-FC, and mouse or sheep RBC. Except for the lack of CIg in the in vitro cells, the marker pattern corresponded to that of Hodgkin's and Sternberg-Reed cells in biopsy material. The phenotype was not that of B cells, T cells, myeloid cells, monocytes, or macrophages. (26 Refs)

63. DISTRIBUTION OF HLA CLASS 1 ANTIGENS IN NORMAL HUMAN TISSUE AND IN MAMMARY CANCER.

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J Clin Pathol; 34(7):779-784 1981

With a monoclonal antibody which reacts with all HLA Class 1 antigens it was found that these antigens are not uniformly distributed in all nucleated cells. Rather HLA Class 1 antigens are restricted in their distribution to lymphoid cells, endothelial cells of small vessels, and certain epithelia including mammary duct cells. These antigens were not detected on hepatocytes, specialized cells of the central nervous system, or on the tumor cells of 8 out of 17 human mammary cancers. Given the hypothesis that T cells only respond to foreign antigens on cells which share a common major histocompatibility antigen, these results imply that the T cell responses to viral infections of hepatocytes - for example, hepatitis B virus and the CNS - for example, subacute sclerosing encephalitis, are mediated through an antigen system other than HLA Class 1. The absence of HLA Class 1 antigen on many mammary cancer cells may be of prognostic significance if T cell modulation of tumor growth is mediated through this class of antigens. (Author abstract) (19 Refs)

64. H-2 ANTIGENS INCORPORATED INTO PHOSPHOLIPID VESICLES INTERACT SPECIFICALLY WITH ALLOGENEIC CYTOTOXIC T LYMPHOCYTES.

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Cell Immunol; 63(1):42-56 1981

Subcellular fractions containing different H-2 antigens were tested for their ability to inhibit specific T cell-target cell conjugate formation. H-2-containing membrane vesicles, lentil-lectin-purified H-2 antigens solubilized with detergent (referred

to in the text as high-density fraction) or incorporated into lipid vesicles, inhibited T cell-target cell conjugate formation effectively and specifically. However, two- to three-fold more protein was required to inhibit T cell-target cell conjugate formation when detergent-solubilized lentil-lectin-purified H-2 antigens were tested. This sugg ests that a lipid matrix is advantageous for interaction with anti-H-2 T-cell receptors. Experiments were also undertaken to demonstrate specific binding of liposomes containing 125I-labeled H-2 antigen to anti-H-2-specific cytotoxic T lymphocytes (CTLs). The binding of the 125I-labeled H-2-containing liposomes was saturable and was specifically inhibited by unlabeled H-2 antigens. Monospecific anti-H-2 sera specifically inhibited the binding of liposomes containing H-2 antigen to the CTLs. The results suggest that a specific interaction can occur between serologically defined H-2 antigens and the receptor of anti-H-2 CTLs. (Author abstract) (29 Refs)

65. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Oncology Overview covers the purification, localization, structure, and function of the 220,000 dalton cell surface transformation-sensitive protein fibronectin (also known as LETS protein, CIg, soluble fibroblast antigen, cell surface protein, and zeta protein). The dramatic reduction of cell surface fibronectin which occurs during transformation may become a useful marker characteristic in correlations of tumorigenicity and the transformed phenotype. The expression of fibronectin on a variety of normal and transformed cells, and the control of expression, are reviewed. Other areas of fibronectin research which are covered include: the influence of mitogenic proteases on fibronectin in relation to cell growth control; fibronectin interactions with collagen and proteoglycan; ultrastructure of intercellular fibronectin matrix; fibronectin's role in cell-cell adhesion, cell-substratum adhesion, cell surface centripetal flow inhibition, cell motility and restoration of cultured cells to normal phenotype; and differentiation-associated alterations in cell surface fibronectin. Also included are studies of the transformation-sensitive cell surface proteins which are relevant to fibronectin research.

66. INDUCTION OF COMPLEMENT RECEPTORS IN HUMAN CELL LINES DERIVED FROM UNDIFFERENTIATED LYMPHOMAS.

Jaffe ES, Smith SA, MaGrath IT, Freeman CB, Alabaster O, Sussman EH
Lab. Pathology, NCI, Building 10 Room 2N110, Bethesda, MD, 20205
Lab Invest; 45(3):295-301 1981

Two Epstein-Barr nuclear antigen-negative cell lines, EW36 and CA46, derived from human undifferentiated lymphomas were exposed to the methylxanthines theophylline and 3-isobutyl-1-methylxanthine. Both compounds markedly increased the proportion of cells which bears complement receptors, whereas other surface markers such as surface immunoglobulin and IgG Fc receptors were unchanged. The inducing agents hexamethylene bisacetamide and dimethylsulfoxide had a similar effect, but other compounds known to alter intracellular cyclic AMP had no effect on surface markers. The expression of complement receptors first appeared at 8 to 10 hr and was dependent upon the continued presence of theophylline in the tissue culture medium. Other effects of the methylxanthine derivatives tested included inhibition of DNA synthesis and a reduction in mean cellular vol. However, inhibition of growth per se did not result in complement receptor induction. These data suggest that the differentiation agents active in this system may be useful tools in the study of human lymphoid malignancies. (Author abstract) (22 Refs)

67. A NOVEL HUMAN T CELL ANTIGEN PREFERENTIALLY EXPRESSED ON MATURE T CELLS AND SHARED BY BOTH WELL AND POORLY DIFFERENTIATED B CELL LEUKEMIAS AND LYMPHOMAS.

Kamoun M, Kadin ME, Martin PJ, Nettleton J, Hansen JA
Dept. Lab. Medicine, Univ. Washington SB-10, Seattle, WA, 98195
J Immunol; 127(3):987-991 1981

A new lymphocyte differentiation antigen shared by all normal T cells and some malignant B cells was defined by a monoclonal antibody designated 12.1. This antibody reacted with all peripheral blood T cells but not with normal B cells and B cell lines. Analysis with a fluorescence activated cell sorter showed that the expression of 12.1 antigen changes during T cell maturation. Most thymocytes, blasts of acute T cell leukemia, and cells from established leukemic T cell lines bear a small amount of 12.1 antigen. In contrast the majority of peripheral blood T cells, activated T cells, and leukemic T cells of the Sezary syndrome bear a large amount of 12.1 antigen. Unexpectedly, antibody 12.1 reacted with leukemic cells from most patients with B-type chronic lymphocytic leukemia (CLL) and some patients with lymphosarcoma cell leukemia (LSCL). Among these leukemias, expression of the 12.1 antigen was not correlated with the stage of B cell maturation, with the amount of surface immunoglobulin on the cells, or with the presence or absence of monoclonal gammopathy. In a comparative serologic analysis the antigen defined by antibody 12.1 was distinct from the p67 T cell antigen (defined by monoclonal antibody 10.2) that is also known to be expressed by B-type CLL cells. (Author abstract) (22 Refs)

68. LEUKAEMIC LIVER INFILTRATION IN AKR MICE PREMATURELY INDUCED BY IMMUNIZATION WIT H HUMAN OR ALLOGENEIC LIVER PROTEIN.

Rowe AE, Cowan BM, Eddleston AL, Thomson AD
(c/o Thomson) Dept. Gastroenterology, Greenwich District Hosp., Vanbrugh Hill, London S10 9HE, England
Clin Exp Immunol; 45(2):305-307 1981

An attempt was made to produce a model of autoimmune hepatitis in AKR mice by immunization with allogeneic liver extract or a purified (human) liver-specific lipoprotein (LSP). Although a mononuclear infiltrate was found in the liver in recipients of purified liver antigen and to a lesser degree in recipients of allogeneic extract, this was associated with the development of an acute thymus-derived leukemia. This mouse strain is normally susceptible to leukemia after a latent period of approx 6 to 9 mo but the immunization schedule markedly reduced the age of onset of this disease. (Author abstract) (11 Refs)

69. TISSUE SPECIFICITY AND CELLULAR DISTRIBUTION OF NOVIKOFF HEPATOMA ANTIGENIC PROTEINS P39, P49, AND P56.

Schmidt WN, Stryjecka-Zimmer M, Glass WF, Briggs RC, Hnilica LS
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232

J Biol Chem; 256(15):8117-8123 1981

Three Novikoff hepatoma protein antigens (approx Mr = 39,000, 49,000 and 56,000) were partially purified from Novikoff hepatoma chromatin. Rabbit antiserum to these three proteins was used to examine various rat tissues for the presence of these antigens. Immunological specificity of the antiserum was assessed using quantitative microcomplement fixation assay or by visualization of the immunoreactive complexes with peroxidase-antiperoxidase procedure after transferring the electrophoretically separated proteins to nitrocellulose sheets. The immunoreactivity was localized with the three proteins p39, p49, and p56 in Novikoff hepatoma. The p56 protein was found to be present in normal rat liver, 24-hr regenerating rat liver, fetal rat liver, or kidney, albeit in much smaller amounts as found in Novikoff hepatoma. The p49 and p39 antigens were specific for Novikoff hepatoma. Immunoabsorption experiments confirmed the specificity of this antiserum. Assessment of various subcellular fractions of Novikoff hepatoma revealed that the p39, p49, and p56 protein antigens are present in the cytoplasmic fractions as well as in isolated chromatin. (Author abstract) (34 Refs)

70. DIAGNOSIS OF BREAST CARCINOMA WITH THOMSEN-FRIEDENREICH (T) ANTIGEN AND HUMAN ANTI-T ANTIBODY.

Springer GF, Murthy SM, Desai PR, Wurtz K, Black S, Scanlon EF
Dept. Surgery, Northwestern Univ., Evanston, IL

Breast; 7(3):24-30 1981

Delayed-type skin hypersensitivity (DTH) to T antigen was measures in 102 patients with ductal breast carcinoma, 24 patients with lobular and two patients with tubular breast carcinoma, and 148 patients with benign breast diseases. Cell-mediated T antigen immunity was measured in vitro b y leukocyte migration inhibition. T-specific immunoreactive structures were found on 93% of breast carcinoma tissues, all distant metastasis tissues, all cultured breast carcinoma-derived cell lines, on adenocarcinoma tissues from other sites, and on four out of six melanomas. T-specific structures were not detected in 29 of 31 benign breast lesions or any of four mammoplasty tissues. Patients showing apparent false positives had hyperplastic conditions, which were later rediagnosed as carcinomas. Data from patients after surgery suggest that T-specific DTH may be useful in monitoring treatment of breast cancer treatment, since DTH disappears in patients not showing recurrence of tumors. Apparently T-specific structures occur in normal tissues in a covered form. In adenocarcinoma tissues these structures are in an exposed, reactive form, which may serve diagnostic purposes. The T antigen may be useful in adjuvant therapy. (31 Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CANCER

1. USE OF AN ELECTROIMMUNODIFFUSION METHOD ON CELLULOSE ACETATE FILMS FOR THE DETECTION OF ANTIGENICITY IN HUMAN BREAST CANCER THAT IS RELATED TO THE MAJOR CORE ANTIGEN OF MOUSE MAMMARY TUMOR VIRUS (MUMTV).

Kryukova IN, Komarova E, Zotter S, Grossmann H
All Union Cancer Res. Center, Acad. Medical Sciences, Kashirskoye Chausse 6, Moscow 115478, USSR
Arch Geschwulstforsch; 51(6):517-521 1981

The method developed by Abelev was used for detection of MuMTV-related antigens in tumor tissue and sera of breast cancer patients. The highly sensitive electroimmunodiffusion method on acetate films employed isotachophoresis. In 2/5 breast cancer extracts, protein fractions of about 50,000 mol wt exhibited antigenicity related to the major core antigen of MuMTV (p27). This antigenicity was not detected in the patients' sera. (18 Refs)

2. KAPOSI'S SARCOMA. IV. DETECTION OF CMV DNA, CMV RNA AND CMNA IN TUMOR BIOPSIES.

Boldogh I, Beth E, Huang ES, Kyalwazi SK, Giraldo G
(c/o Huang) Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514
Int J Cancer; 28(4):469-474 1981

In order to determine whether human cytomegalovirus-(CMV) DNA homologous sequences as well as CMV-specific RNA(s) and antigen(s) exist in tumor biopsies of Kaposi's sarcoma (KS) DNA-DNA reassociation, RNA-DNA in situ cytohybridization and anticomplement immunofluorescence test (ACIF) tests were applied. Three of 10 DNAs extracted from Kaposi sarcoma biopsies contained DNA sequences homologous to radioactively labeled human CMV DNA probe. The amount of CMV DNA in these sarcoma tissues was calculated to range from 0.7 to 1 genome equivalent per diploid cell. The presence of virus-specific RNA was also demonstrated in sections from 5 of 10 tumor biopsies. CMV-determined nuclear antigen(s) (CMNA) present in variable degrees were also demonstrated. In contrast, we could not detect any herpes simple virus type II (HSV-2) or Epstein-Barr virus (EBV) DNA sequences in DNA of these tumor biopsies. Furthermore, there were no detectable HSV-2 or EBV-specific RNA or virus-specific antigens in sections of these biopsies. These results provide new lines of evidence for the relationship between CMV and Kaposi's sarcoma. (Author abstract) (34 Refs)

3. DISCUSSION ON ETIOLOGY (KAPOSI'S SARCOMA).

Olweny CL, Giraldo G, Vogel CL, Geser A, Kigongo, Kungu A, Lothe F, Owor R
Uganda Cancer Inst., Kampala, Uganda
Antibiot Chemother; 29:30-31 1981

The question of second malignancies associated with Kaposi's sarcoma (KS) is discussed with particular reference to five cases seen in a 5-yr-period. It is uncertain whether KS consists of two different diseases; antigen-antibody complexes must be investigated in patients with the regressor type of disease (nodular indolent) and in those with progressive disease (lymphadenopathic, florid, and infiltrative). The same etiological agent may cause different clinical presentation depending on host response to the agent. A disease with long incubation period may not exhibit time-space clustering even though it has an infectious etiology. The possibility that the antigens identified in KS are tumor antigens being produced by the tumor but with viral characteristics is currently being researched. (no Refs)

4. KAPOSI'S SARCOMA IN HOMOSEXUAL MEN - A REPORT OF EIGHT CASES.

Hymes KB, Greene JB, Marcus A, William DC, Cheung T, Prose NS, Ballard H, Laubenstein LJ
(c/o Laubenstein), New York Univ. Medical Center, 530 First Ave., New York, NY, 10016
Lancet; 2(8247):598-600 1981

The clinical findings in eight young homosexual men in New York with Kaposi's sa rcoma showed some unusual features. Unlike the form usually seen in North America and Europe, it affected younger men (4th decade rather than 7th decade); the skin lesions were generalized rather than being predominantly in the lower limbs, and the disease was more aggressive (survival of less than 20 mo rather than 8-12 yr). All eight had had a variety of sexually transmitted diseases. All those tested for cytomegalovirus antibodies and hepatitis B surface antigen or anti-hepatitis B antibody gave positive results. This unusual occurrence of Kaposi's sarcoma in a population much exposed to sexually transmissible diseases suggests that such exposure may play a role in its pathogenesis. (Author abstract) (12 Refs)

5. ETIOLOGICAL IMPLICATIONS ON KAPOSI'S SARCOMA.

Giraldo G, Beth E, Kyalwazi SK
Natl. Cancer Inst. 'Fondazione Pascale', Naples, Italy
Antibiot Chemother; 29:12-29 1981

Multidisciplinary study of 176 cases of Kaposi's sarcoma (KS) was conducted during 1971-1979. Biopsy specimens and sera from KS patients and corresponding controls were collected within five different African Cancer Centers in areas of high and moderate KS incidence. Samples were also collected in various hospitals in areas of France with a low incidence of KS. African KS patients had high antibody titers to cytomegalovirus (CMV), but they were not significantly different from controls in the same regions. A specific serological association of European and American KS with CMV was established. CMV-related antigens were detected in 22% of tumor biopsies and in early passages of cell cultures derived from them. CMV-DNA sequences have been detected in tumor biopsies. Strain K9V CMV has been isolated in a KS-derived tissue culture. In vitro, cells infected with K9V have some of the features of cells transformed by other oncogenic CMV strains. In vivo, K9V induced a fatal lymphoid disease in old world monkeys. Clusters of KS have been observed in the West Nile District of Uganda. A significantly higher incidence of second primary tumor, particularly of the lymphoreticular system, has been observed in KS patients. (32 Refs)

6. EPSTEIN-BARR VIRUS IN A MALIGNANT LYMPHOPROLIFERATIVE DISORDER OF B-CELLS OCCURRING AFTER THYMIC EPITHELIAL TRANSPLANTATION FOR COMBINED IMMUNODEFICIENCY.

Reece ER, Gartner JG, Seemayer TA, Joncas JH, Pagano JS
Dept. Allergy and Clinical Immunology, Montreal Children's Hosp. Res. Inst., McGill Univ., Montreal, Quebec, H3H 1P3, Canada
Cancer Res; 41(11,part1):4243-4247 1981

A fatal disseminated polyclonal malignant lymphoproliferative disorder of B-cells (immunoblastic sarcoma) developed shortly after a second thymic epithelial peritoneal implant in a

5-yr-old girl with combined immunodeficiency. The immunodeficiency was characterized by low T-cell numbers and function, very low levels of thymic hormone, dysgammaglobulinemia, and an inability to mount a primary antibody or cell-mediated response to new antigens. At necropsy, the thymus fulfilled morphological criteria for thymic dysplasia. Epstein-Barr virus (EBV) antigen and DNA were identified in neoplastic infiltrates in the lymph nodes and thymus by immunofluorescence for the EBV nuclear antigen and by EBV-specific complementary RNA/DNA hybridization. No antibodies to nuclear antigen, early antigen, or viral capsid antigen of EBV were identified in the serum. The concurrence of these events suggests that the thymic epithelial implant itself may have been instrumental in the pathogenesis of this neoplasm. It is proposed that the thymus may have provided factors which indirectly potentiated the proliferation of EBV-infected B-cells, possibly by induction of nonspecific T-helper cells and perhaps through other thymic humoral factors. It is suggested that some forms of immunoblastic sarcoma, even when polyclonal, and especially those which arise in immunocompromised hosts, may, in some instances, represent an opportunistic form of EBV-induced B-cell neoplasia. (Author abstract) (39 Refs)

7. EPSTEIN-BARR VIRUS INFECTION AND NEOPLASIA.

Sprinkle PM, Veltri RW
Dept. Otolaryngology, West Virginia Univ., Morgantown, WV
Otolaryngol Head Neck Surg; 89(4):542-544 1981

Conclusive serological data of activation of Epstein-Barr virus (EBV) is reported showing persistently elevated early antigen (EA) titers prior to and following malignant transformation in a 6-yr-old boy. Heterophil-negative EBV disease characterized by lymphadenopathy and recurrent tonsillitis developed in the child 1 mo after his sister died with heterophil-negative infectious mononucleosis. Epstein-Barr nuclear antigen (EBNA) and EA were detected in many B-lymphocytes present in each of the same tissue specimens. One yr later, rebiopsy of the cervical nodes revealed typical Hodgkin's disease. EBNA and EA were found in hilar and celiac lymph nodes as well as in splenic lymphocytes. Serum antibody study demonstrated a 1:640 EA and 1:2,560 viral capsid antigen-IgG specific antibody to their EBV-coded antigens. Before and after the diagnosis of Hodgkin's disease, however, the patient's EA titers were persistently elevated and remained so. The child was alive with a poor prognosis after multiple chemotherapy courses and two courses of radiotherapy. The child's mother died in the interim with undifferentiated lymphoma. (16 Refs)

8. FATAL EPSTEIN-BARR VIRUS INFECTION IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN REMISSION.

Look AT, Naegele RF, Callihan T, Herrod HG, Henle W
Div. Hematology Oncology, St. Jude Children's Res. Hosp., P.O. Box 318, Memphis, TN, 38101
Cancer Res; 41(11,part1):4280-4283 1981

A 9-yr-old white boy developed a fatal primary Epstein-Barr virus (EBV) infectio n while receiving chemotherapy for acute lymphoblastic leukemia in remission. Histopathological findings at the height of the proliferative phase of the illness were compatible with a virally induced hemophagocytic syndrome. The infection spontaneously converted to complete aplasia of the bone marrow and lymph nodes. Serological studies disclosed that the patient had no antibodies to EBV prior to the infection, but during the acute phase he showed a spectrum and titers of antibodies to EBV-specific antigens characteristic of a current primary EBV infection. A lymph node biopsy obtained 5 wk after onset revealed Epstein-Barr nuclear antigen in approx 50% of the cells. The boy's condition deteriorated rapidly, with disseminated candidiasis resulting in cardiorespiratory failure and death. Lymph nodes obtained at autopsy no longer contained Epstein-Barr nuclear antigen-positive cells. (Author abstract) (24 Refs)

9. SUMMARY: SYMPOSIUM ON EPSTEIN-BARR VIRUS-INDUCED LYMPHOPROLIFERATIVE DISEASES IN IMMUNODEFICIENT PATIENTS.

Klein G, Purtilo D
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4302-4304 1981

The possibility that the X-linked lymphoproliferative syndrome, renal transplant lymphomas, and other lymphomas in immunodeficient patients originate in proliferating Epstein-Barr virus (EBV)-carrying lymphoid cells is discussed. Evidence for this association included the detection of EBV nuclear antigen (EBNA) in virus-transformed cells and changes in EBV antibody titers in immunodeficiency conditions. Defects of the T-cell system were associated with increased titers against EBV early and viral capsid antigens and decreased anti-EBNA titers. Chronic infectious mononucleosis patients and X-linked lymphoproliferative syndrome patients showed marked impairment of all effector mechanisms involved in the rejection of EBV-carrying cells. (23 Refs)

10. CLINICAL SPECTRUM OF LYMPHOPROLIFERATIVE DISORDERS IN RENAL TRANSPLANT RECIPIENTS AND EVIDENCE FOR THE ROLE OF EPSTEIN-BARR VIRUS.

Hanto DW, Frizzera G, Purtilo DT, Sakamoto K, Sullivan JL, Saemundsen AK, Klein G, Simmons RL, Najarian JS
Dept. Surgery, Univ. Minnesota, Mayo Memorial Building, 420 Delaware St. South East, Minneapolis, MN, 55455
Cancer Res; 41(11,part1):4253-4261 1981

Six renal transplant recipients with abnormal lymphoproliferative disorders were studied in an attempt to define their clinical features and the role of Epstein-Barr virus (EBV) in their pathogenesis. Patients were either teenage (3) or in the sixth decade (3). The younger patients presented an av of 3 mo after transplantation with fever, sore throat, and lymphadenopathy; had been markedly immunosuppressed; frequently had preceding or concomitant cytomegalovirus infections; and two of three had a rapidly fatal course. The older patients presented an av of 5 yr after transplantation while on maintenance immunosuppressive drugs; in two of three cases with an oropharyngeal tumor; and had a more indolent, but frequently fatal, clinical course. The most frequent sites of biopsy-proven involvement in these patients were lymph nodes (3), the oropharynx (3), liver (3), bone marrow (3), transplanted kidney (3), colon (2), and central nervous system (2). EBV-specific antibody titers including anti-viral capsid antigen IgG, anti-viral capsid antigen IgM, anti-early antigen, and anti-Epstein-Barr nuclear antigen were serially measured in all patients. Four patients demonstrated serological evidence of a primary (1) or reactivation (3) EBV infection. No patient had significant changes in anti-early antigen or anti-Epstein-Barr nuclear antigen titers. All three patients tested for oropharyngeal shedding of EBV were positive. A touch imprint of one tumor was stained for the presence of Epstein-Barr nuclear antigen, and a majority of cells were positive. EBV complementary RNA/

DNA filter hybridization and/or viral DNA/DNA reassociation analysis performed on tumor biopsy specimens in five patients demonstrated multiple EBV genome equivalents per cell in all eight specimens tested. Clinical, pathological, serological, and molecular hybridization studies provide substantial evidence that EBV was the cause of these lymphoproliferative disorders occurring after renal transplantation. Impaired host defenses allow the EBV-transformed B-lymphocytes to escape normal control mechanisms. This impairment is variable and influenced by many factors resulting in the observed spectrum of disease. Cytogenetic changes, however, may also be important. (Author abstract) (45 Refs)

11. DISCRIMINANT ANALYSIS OF THE FACTORS CAUSING HEPATOMA IN YAMANASHI PREFECTURE (MEETING ABSTRACT).

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Nippon Eiseigaku Zasshi; 36(1):187 1981

The data for 62 hepatoma patients and 62 control patients were selected from the patient-control studies conducted in Yamanashi Prefecture for about 2.5 yr beginning in 1977. Five risk factors, hepatitis B surface (HBs) antigen (X1), history of schistosomiasis japonica (X2), daily intake of alcohol (X3), history of transfusion (X4) and schistosoma skin test (X5) were selected. The absence of a factor was designated as 1 and its presence as 2 on a computer, and the discriminant coefficient of each factor was calculated by using the Statistical Packages for the Social Sciences Program of the Computer Center, University of Tokyo. A significant difference between the hepatoma group and control group was obtained for the scores of the HBs antigen, history of schistosomiasis japonica and daily intake of alcohol. The schistosoma skin test alone showed a negative correlation, and this may not be unrelated to the immunopotential of the hepatoma group. The discriminant score for the hepatoma and control groups were obtained and the cumulative percentages were calculated. If the positive discriminant score was assigned to the hepatoma group and negative discriminant score to the control group, the predicted results agreed with the actual results in 99 out of 124 patients. There were 19 false-negative entries and 6 false-positive entries. The discriminant formula Y = 1.80X1 + 1.67X2 + 1.04X3 + 1.00X4-0.74X5-6.00 was considered to be effective for predicting hepatoma. (no Refs) (In JPN)

12. SEROEPIDEMIOLOGIC STUDIES IN HODGKIN'S DISEASE.

Kokosha LV, Lapin BA, Lebedev VN, Danilova NV, Arshba NN, Bologov VN
Lab. Experimental Oncology, Inst. Experimental Pathology and Therapy, Sukhumi, USSR
Probl Gematol Pereliv Krovi; 26(8):12-16 1981

To evaluate the possibility of horizontal transmission of Epstein-Barr virus (EBV), antibodies against capsid antigen of EBV were determined in 109 patients with Hodgkin's disease (HD) and in 67 relatives of 46 patients. High titers of antivirus antibodies were recorded in 70% of the patients with HD. The highest titers were recorded in the patients with lymphoid exhaustion (1:256, compared with 1:97 in lymphoid predominance and mixed cell variant, and 1:49 in nodular sclerosis). The titers of antibodies against EBV antigen in the relatives were significantly greater that that in healthy donors (1:69 and 1:6, respectively). (34 Refs) (In RUS)

13. DEMONSTRATION OF SV40-RELATED TUMOUR ANTIGEN IN HUMAN MENINGIOMAS BY DIFFERENT HAMSTER SV40-T-ANTISERA.

Zimmermann W, Scherneck S, Geissler E, Nisch G
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Acta Virol (Praha); 25(4):199-204 1981

Three of five human meningiomas tested in cell culture expressed SV40-related tumor (T) antigen as measured by indirect immunofluorescence with four different hamster anti-SV40 tumor sera. The percent of T-antigen-positive nuclei varied depending on the antisera used. In one case (meningioma G S), only 25% of the T-antigen-positive nuclei detected with one antiserum could be demonstrated with another serum. The possible explanations are discussed. None of the meningioma cell cultures tested expressed SV40-related viral capsid (V) antigen. (Author abstract) (20 Refs)

14. A NEW VIEW OF THE ETIOLOGY OF NASOPHARYNGEAL CARCINOMA.

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Prev Med; 10(5):614-622 1981

Epidemiological studies showed a high incidence of nasopharyngeal carcinoma (NPC) in southern regions of China. Also found in these regions are plants of the Euphorbiaceae family, inclu ding Croton tiglium (the source of croton oil) and other species used as herbal drugs. Interaction of herbal drugs and anti-Epstein-Barr virus (EBV) titers was noted. Use of the herbal drugs was related to nasal infection by microbes such as Fusobacterium. The combined effects of drug use and EBV induction were synergistic rather than additive. Fusobacteria in culture produced n-butyric acid, which had a low, but definite EBV-inducing activity in human lymphoblastoid P3HR-1 cells. Combined treatment with nanog concentrations of croton oil and n-butyrate produced marked increase in EBV antigens in EBV genome-carrying P3HR-1 and Raji cells. Apparently EBV is induced and activated by the combination of bacterial fatty acid and herbal oils. It is suggested that the activated EBV then initiates steps resulting in NPC. (33 Refs)

15. AN OVERVIEW OF IMMUNOTHERAPY, ESPECIALLY OF BREAST CANCER.

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Comment Res Breast Dis; 2:103-132 1981

Immunotherapy, particularly as applied to treatment of breast cancer, is reviewed. Parameters of immune responsiveness to breast cancer, such as lymphocyte transformation and infiltration, response to skin test antigens, and peripheral lymphocyte counts, are described. The nature of viral antigens in breast cancer is discussed. Suppressors and suppressor cells, including non-T cell suppressor cells, are discussed. Active, adoptive, and passive immunotherapies are detailed, including use of Corynebacterium parvum, BCG, levamisole, immune RNA, interferon, glucan, and transfer factor. Future research into the isolation of those components of biological agents, such as BCG and C parvum, which produce particular effects on immune response, is urged. (127 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

16. PHOSPHORYLATION PATTERNS OF TUMOR ANTIGENS IN CELLS LYTICALLY INFECTED OR TRANSFORMED BY SIMIAN VIRUS 40.

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J Virol; 40(1):28-44 1981

The phosphorylation sites of simian virus 40 (SV40) large tumor (T) antigens have been analyzed by partial proteolysis peptide mapping and phosphoamino acid analysis of the resulting products. At least four sites were found to be phosphorylated. An amino-terminal part of the molecule contained both phosphoserine and phosphothreonine. One phosphothreonine residue was located in the proline-rich carboxy-terminal end of the molecule, either at position 701 or at position 708. The mutant dl1265, which is defective in adenovirus helper function, lacked this phosphorylation site. In addition, the carboxy-terminal part of the molecule contained phosphoserine at a more central position. T-antigen-associated protein s of SV40-transformed cells (nonviral T; 51,000 to 55,000 daltons) also contained multiple phosphorylation sites involving at least two serine residues in mouse antigens and an additional threonine residue in rat, human, and monkey antigens. The latter residue and at least one phosphoserine residue were located near one terminus of the human NVT molecule. We did not find any evidence for phosphorylation of tyrosine residues in any of the multiple species of either large T or nonviral T molecules. Several forms of large T antigens were extracted from both SV40-transformed and SV40-infected permissive and nonpermissive cells, and their phosphorylation patterns were compared. No evidence was found for a different phosphorylation pattern of T antigens in transformed cells. (Author abstract) (62 Refs)

17. ISOLATION OF A SV40-LIKE VIRUS FROM A PATIENT WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY.

Scherneck S, Geissler E, Janisch W, Rudolph M, Vogel F, Zimmermann W
Central Inst. Molecular Biology, DDR 1115, Berlin-Buch, E. Germany
Acta Virol (Praha); 25(4):191-198 1981

A SV40-like virus was isolated from the brain of a patient with progressive multifocal leukoencephalopathy. The virus was antigenically and serologically indistinguishable from SV40 wild type. A unique difference from SV40 was its ability to grow on human glial and CV-I monkey cells. The mol wt of the viral DNA was very similar to that of SV40 DNA and the DNA cleavage patterns obtained after digestion with Hind II and Hind III restriction endonucleases were indistinguishable from those of SV40. (Author abstract) (30 Refs)

18. DOES SIMIAN VIRUS 40 T ANTIGEN UNWIND DNA?

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J Biol Chem; 256(19):10156-10160 1981

Recently developed techniques allow rapid and accurate determination of protein-induced DNA unwinding. We have used such techniques to determine whether SV40 T antigen unwinds DNA. Assays were performed with purified wild type T antigen, D2 protein, and the SV80 T protein over a wide range of protein concentrations. Additionally, several DNA templates were used, including SV40 DNA, pBR322 DNA, and two plasmid DNAs containing one and three copies of the SV40 origin of replication. None of the purified proteins showed unwinding activity either in the presence or absence of ATP and Mg++. As a positive control, we found that unwinding of pBR322 DNA by Escherichia coli RNA polymerase occurred under identical assay conditions. Protein-DNA interactions that involve unwinding of the helix are sensitive to the superhelical density of the DNA. Using a filter binding assay, we found that the efficiency of the binding of T antigen to the viral origin of replication does not depend upon the topological state of the DNA. Thi s result further supports our conclusion that SV40 T antigen is not an unwinding protein. (Author abstract) (32 Refs)

19. SIMIAN VIRUS 40 EARLY MRNA'S CONTAIN MULTIPLE 5' TERMINI UPSTREAM AND DOWNSTREAM FROM A HOGNESS-GOLDBERG SEQUENCE; A SHIFT IN 5' TERMINI DURING THE LYTIC CYCLE IS MEDIATED BY LARGE T ANTIGEN.

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J Virol; 40(1):224-240 1981

We have used primer-directed synthesis, separation, and sequencing of cDNA's to identify and localize the 5' termini of simian virus 40 early mRNA's. We have examined polyadenylated RNAs obtained from whole cytoplasm and polysomes of two transformed lines and from the cytoplasm of infected cells early and late in the lytic cycle, and we have attempted to correlate the results of our cDNA analyses with recent analyses of early cap structures. We have found that early mRNA's from transformed cells have three principal 5' termini, at residues 5,150, 5,154, and 5,155, with terminal transcribed sequences of CU, GC, and GG, respectively. These termini lie 21 to 26 nucleotides downstream from the early Hogness-Goldberg sequence. Transformed cell early mRNA's also contain a series of less abundant 5' termini that are copied from DNA sequences as far as 80 nucleotides downstream and a minimum of 70 to 75 nucleotides upstream from the Hogness-Goldberg sequence. The templates for the upstream 5' termini and the late simian virus 40 mRNA's overlap by a minimum of 60 to 65 nucleotides. Early mRNA's isolated from cells early in infection contain the same three principal 5' termini and downstream minor 5' termini as transformed cell mRNA's, but they lack 5' termini upstream from the Hogness-Goldberg sequence. With the onset of the late lytic phase, there is a progressive decrease in the utilization of the three principal 5' termini and additional downstream 5' termini and a progressive increase in the utilization of four major termini at residues 5,190 to 5,194, which are 10 to 15 nucleotides upstream from the Hogness-Goldberg sequence. This shift is evident in cells infected with a tsA mutant at the permissive temperature, but is aborted by growth at or shift-up to a restrictive temperature. Thus, this shift is mediated by the gene A product, large T antigen. We present two models, which are mutually exclusive, to account for the role of T antigen in the early-late shift. One involves transcription late in infection on a new DNA template synthesized during DNA replication. The second involves inhibition of initiation of early transcription at residues 5,150 to 5,155 and other downstream sites and a shift of transcription initiation principally to the upstream sites as a result of the binding of T antigen to two sites on simian virus 40 DNA downstream from the Hogness-Goldberg sequence. (Aut hor abstract) (53 Refs)

20. SEQUENTIAL TRANSCRIPTION-TRANSLATION OF SIMIAN VIRUS 40 BY USING MAMMALIAN CELL EXTRACTS.

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Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Mol Cell Biol; 1(10):919-931 1981

The expression of Simian virus 40 (SV40) was studied using the current technologies of recombinant DNA and in vitro transcription systems. The in vitro transcription of specific SV40 RNAs is described. A polypeptide comigrating with the 94K T antigen of SV40 was not present in products transcribed from Eco-RI-, PstI-, or TaqI-cleaved DNA. However, if a small fraction of the RNA transcribed from the Eco-RI-cleaved DNA had been processed by excision of the intervening sequences between 0.60 an 0.53 monitor units, synthesis of T (94K) would have been possible. Synthesis of the large T family of polypeptides is described. When the relative efficiencies of in vivo- and in vitro-synthetized RNA were quantitated, it was determined that in vitro small tumor antigen t messenger RNA (mRNA) is more efficiently translated than in vivo t mRNA. The translatability of the in vitro transcripts from the SV40 late regions was examined; the synthesis of the viral capsids VP1, VP2, and VP3 from RNA transcribed in vitro was studied. By using DNA templates cleaved within the late region, information concerning the identity of the transcripts that served as VP1, VP2, and VP3 messages was obtained. RNAs synthesized in vitro were fractionated by size to allow the direct identification of VP1, VP2, VP3, and t mRNAs. Other topics discussed include the efficiency of in vitro RNAs as messages, assay for RNA splicing, initiation at internal AUG codons, synthesis of polypeptides by minor transcripts (assay for proteins specified by complementary DNA clones), and lack of termination in the inhibition of translation. (32 Refs)

21. EXPRESSION OF SV40 T ANTIGEN POLYPEPTIDES IN CELLS BIOCHEMICALLY TRANSFORMED BY PLASMIDS CONTAINING THE HERPES SIMPLEX VIRUS THYMIDINE KINASE GENE AND THE GENOME OF AN SV40TSA MUTANT.

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Int J Cancer; 28(4):485-496 1981

To study the expression of SV40 tsA genomes that had been non-selectively introduced into mouse cells, SV40 tsA207 DNA was cleaved with BamH I and ligated to BamH I-cleaved plasmid pAGO DNA, which contains a functional HSV-I thymidine kinase (TK) gene in the form of a 2 kbp Pvu II fragment inserted at the Pvu II site of pBR322. Recombinant plasmids (11-12 kbp) were isolated and amplified in Escherichia coli K12 strain RRI. Restriction nuclease analyses demonstrated that recombinant plasmids pSB15 and pSB10 contained intact SV40 genomes with the polarity of transcription oriented in the same direction (clockwise) or the opposite direction (counterclockwise), respectively, in relation to that of the HSV-I TK gene. Cla I-cleaved pSB10 and pSB15 DNAs were used to transform LM(TK-) cells to TK+. Serological and disc PAGE analyses showed that clonal lines transformed by these plasmids all expressed the selected marker, SHV-1 TK. Molecular hybridization experiments showed that transformed clonal lines TF pSB10 C7 and TF pSB15 C10 had integrated intact SV40 genomes at one integration site, TF pSB10 C3 had integrated an SV40 genome with a small deletion near the BamH I site, but TF pSB15 C1 had integrated a plasmid from which most of the SV40 nucleotide sequences had been deleted. IF assays with hamster anti-SV40 tumor sera showed that TF pSB10 C7 and TF pSB15 C10 strongly expressed SV40 T antigens in over 90% of the cells, TF pSB10 C3 expressed SV40 T antigens in a minority of the cells, and TF pSB15 C1 did not express SV40 T antigens at all. [35S]-methionine labeling and immunoprecipitation experiments showed that at 36.5 C: (1) TF pSB10 C7 and TF pSB15 C10 expressed 92K and 20K mol wt species of SV40 T antigens and 50-55K cellular protein; (2) expression of all three was reduced in TF pSB10 C3 cells; and (3) TF pSB15 C1 expressed none of the SV40 T antigens, nor did parental LM(TK-) or TF 8-2 transformed cells (which contained the HSV-1 TK gene but not SV40 DNA). At 40 C, labeling of the 50-55K cellular protein was markedly reduced in TF pSB10 C7 and pSB15 C10 cells. The results suggest that SV40 large T antigen (92K) induces and/or stabilizes the 50-55K cellular protein in these mouse cells. (Author abstract) (53 Refs)

22. DIFFERENTIAL IMMUNOLOGIC REACTIVITY AND PROCESSING OF GLYCOPROTEINS GA AND GB OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 MADE IN VERO AND HEP-2 CELLS.

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Proc Natl Acad Sci USA; 78(8):5202-5206 1981

Herpes simplex virus Types 1 and 2 (HSV-1 and HSV-2, respectiely) specify five major glycoproteins designated as gA, gB, gC, gD, and gE. Previous studies have shown that gA and gB differ in electrophoretic mobility but not in reactivity with antisera prepared to each of these glycoproteins. Moreover, gA and gB of HSV-1 crossreact in serologic tests with the corresponding glycoproteins of HSV-2. In this paper, we report on the reactivities of gA and gB of HSV-1 and HSV-2 with 24 independently derived monoclonal antibodies reactive with these antigens. Our results show the following: (i) Electrophoretic mobilities of HSV-1 and HSV-2 glycoproteins gA and gB made in HEp-2 cells are significantly less than those made in Vero cells. (ii) All monoclonal antibodies precipitated both gA and gB made in infected HEp-2 cells. These include 12 monoclonal antibodies that neutralized virus and 12 that did not. (iii) HSV-2 glycoproteins gA and gB made in HEp-2 cells contain type-specific domains. However, monoclonal antibodies produced by one clone directed to these domains did not react with glycoproteins made in Vero cells. (iv) Lysates of infected Vero cells contain three lower mol wt polypeptides that also reacted with monoclonal antibodies directed to glycoproteins gA and gB. These polypeptides are virus specific inasmuch as those specified by HSV-1 differ in electrophoretic mobilities from those specified by HSV-2. These polypeptides are absent in lysates of HEp-2 cells. (Author abstract) (21 Refs)

23. FOCUS FORMATION AND NEOPLASTIC TRANSFORMATION BY HERPES SIMPLEX VIRUS TYPE 2 INACTIVATED INTRACELLULARLY BY 5-BROMO-2'-DEOXYURIDINE AND NEAR UV LIGHT.

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Dept. Comparative Medicine and Biochemistry, Johns Hopkins Medical Inst., Baltimore, MD, 21205
J Virol; 40(1):289-300 1981

The induction of focus formation in low serum and of neoplastic transformation of Syrian hamster embryo cells was examined after the expression of herpes simplex virus Type 2 functions. Syrian hamster embryo cells infected at a high multi-

plicity (5 PFU/cell) with 5-bromo-2'-deoxyuridine-labeled herpes simplex virus Type 2 (11% substitution of thymidine residues) were exposed to near UV light irradiation at various times postinfection. this procedure specifically inactivated the viral genome, while having little, if any, effect on the unlabeled cellular DNA. Focus formation in 1% serum and neoplastic transformation were observed in cells exposed to virus inactivated before infection, but the frequency was enhanced (15-to 27-fold) in cells in which the virus was inactivated at 4 to 8 hr postinfection. Only 2 of 45 independently isolated foci were capable of establishing tumorigenic lines. The established lines exhibited phenotypic alterations characteristic of a transformed state, including reduced serum requirement, anchorage-independent growth and tumorigenicity. They retained viral DNA sequences and, even at relatively late passage, expressed viral antigens, including ICP 10. (Author abstract) (44 Refs)

24. IDENTIFICATION OF A VIRUS-SPECIFIC POLYPEPTIDE ASSOCIATED WITH A TRANSFORMING FRAGMENT (BGLII-N) OF HERPES SIMPLEX VIRUS TYPE 2 DNA.

Docherty JJ, Subak-Sharpe JH, Preston CM
Microbiology Program, Pennsylvania State Univ., University Park, PA, 16802
J Virol; 40(1):126-132 1981

The BglII N fragment of herpes simplex virus Type 2 (HSV-2) DNA (approx 0.58 to 0.63 map unit) was examined for encoded products. Using plasmid pGZ59, which consists of BglII-N cloned in pAT153, in conjunction with hybrid-arrested translation, mRNA selection, and in vitro protein synthesis, we found that the major translated product of this region has an approx mol wt of 37,800. By further mapping, coding sequences for this polypeptide were located within the region of BglII-N representing approx 0.58 to 0.61 genome map unit. To demonstrate immunological specificity, we used staphylococcal A protein immunoprecipitation with rabbit anti-HSV-1 or HSV-2 sera and antigens from HSV-1 or HSV-2 total mRNA translated in vitro and BglII-N-selected mRNA. The results show that the 37,800-dalton polypeptide has HSV-2 immunological specificity, as it is precipitated with anti-HSV-2 sera but not with anti-HSV-1 or control sera. (Author abstract) (20 Refs)

25. PLEIOTROPIC EXPRESSION OF EPSTEIN-BARR VIRUS DNA IN HUMAN EPITHELIAL CELLS.

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Proc Natl Acad Sci USA; 78(9,part2):5852-5855 1981

We have attempted to establish a system that can be used to study the association of Epstein-Barr virus (EBV) with epithelial cells. Attempts were made to transfect human carcinoma cells with EBV DNA. Successful transfection was confirmed by the expression of EBV-specific early antigen (EA), virus capsid antigen, and the presence of virus DNA. The transfecting preparation contained a mixture of EBV and cellular DNA extracted from two producer cell lines, P3HR-1 and AG-876. Our data suggest that virus DNA obtained from the P3HR-1 nontransforming, EA-inducing strain of EBV was lytically expressed in the epithelial tumor cells. The DNA derived from AG-876 cells, which produce a transforming, non-EA-inducing strain of EBV, also produced a lytic infection. (Author abstract) (21 Refs)

26. DOCUMENTATION OF EPSTEIN-BARR VIRUS INFECTION IN IMMUNODEFICIENT PATIENTS WITH LIFE-THREATENING LYMPHOPROLIFERATIVE DISEASES BY CLINICAL, VIROLOGICAL, AND IMMUNOPATHOLOGICAL STUDIES.

Purtilo DT, Sakamoto K, Saemundsen AK, Sullivan JL, Synnerholm AC, Anvret M, Pritchard J, Sloper C, Sieff C, Pincott J, Pachman L, Rich K, Cruzi F, Cornet JA, Collins R, Barnes N, Knight J, Sandstedt B, Klein G
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Cancer Res; 41(11,part1):4226-4236 1981

Multiple methods, pedigree analysis, clinical evaluation, and Epstein-Barr virus (EBV)-specific serology, EBV DNA hybridization of tissues to probe for viral genome, staining of touch imprints for EBV nuclear-associated antigen, establishment of spontaneous infected B-cell lines from peripheral blood or tissues, examination of peripheral blood smears, and hematopathology studies, were used to study seven patients with the X-linked lymphoproliferative syndrome and seven additional patients with life-threatening EBV-associated diseases. These studies demonstrated EBV in the tissues of all 14 patients and immunodeficient antibody responses to EBV were documented. This virus can produce various life-threatening lymphoproliferative diseases in a variety of immunodeficient patients. (Author abstract) (35 Refs)

27. STRIKING SIMILARITIES ARE EXHIBITED BY TWO SMALL EPSTEIN-BARR VIRUS-ENCODED RIBONUCLEIC ACIDS AND THE ADENOVIRUS-ASSOCIATED RIBONUCLEIC ACIDS VAI AND VAII.

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Mol Cell Biol; 1(9):785-796 1981

The nucleotide sequence of the Epstein-Barr virus genome region coding two small RNAs (EBER 1 and EBER 2) was determined. Both EBERs are coded with a 707-base pair HaeIII/HaeIII fragment near the right-hand end of the EcoRI J/SstI fragment. The 5' terminal oligonucleotide for both is pppAGGAC. Both EBERS show heterogeneity at the 3' end. EBER 1 is 166 (167) nucleotides long. EBER 2 is 172+-1 nucleotides long. Both EBERs are transcribed from the same DNA strand; they are separated by 161 base pairs. The two EBERs show considerable homology, with the greatest in the areas of the 5' termini, around nucleotides 20 and 65, and near the 3' termini. Genes for both EBERs were transcribed by RNA polymerase III. Marked similarities exist between EBERs 1 and 2 and adenovirus-associated RNAs VAI and VAII. All are 160-170 nucleotides long and are transcribed in the same direction on their respective genome strands. Intragenic control regions for the four RNAs are homologous. All four RNAs form nucleoprotein complexes that precipitate with anti-La antibodies associated with systemic lupus erythematosus. Protein from uninfected HeLa cells conferred antigenicity on each of the four RNAs, indicating that antigenicity is conferred by host-cell rather than viral protein. (31 Refs)

28. COMPARISON OF PHOSPHORYLATION OF TWO POLYOMA VIRUS MIDDLE T ANTIGENS IN VIVO AND IN VITRO.

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J Virol; 40(1):184-196 1981

Two species of polyoma virus middle T antigen were detected in both lytically infected and transformed cells by in vitro kinase assay of immunoprecipitates. A minor species with an apparent mol wt of 58,000 (58K) represented less than 10% of the total middle T protein. This species was roughly 10x more active as a phosphate acceptor than was the predominant 56K form. Partial proteolytic mapping experiments showed that the same site was phosphorylated in both species. Mapping of the middle T antigens from a series of deletion mutants suggested that the major site of phosphorylation is tyrosine residue 315. Phosphorylation occurred on both middle T species in vivo, involving sites predominantly other than the tyrosine labeled in vitro. The 56K and 58K middle T forms differed from each other in their in vivo phosphoryla tion patterns. Some phosphate was incorporated into the 58K species in a region of the molecule to which at least part of the apparent mol wt difference could be mapped. hr-t mutant NG-59, which codes for a slightly altered middle T, produced only a single species (56K) which was inactive in the in vitro kinase reaction. Moreover, no 58K species appeared in vivo with this mutant.The hr-t mutants are therefore defective in both aspects of phosphorylation. Phenotypically normal revertant cells of a polyoma transformed line failed to express any middle T antigens or associated kinase activity. (Author abstract) (43 Refs)

29. ANTIBODIES SPECIFIC FOR THE POLYOMA VIRUS MIDDLE-SIZE TUMOR ANTIGEN.

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Proc Natl Acad Sci USA; 78(8):4882-4886 1981

We have obtained antibodies specific for the polyoma virus middle-size tumor antigen (middle T antigen) by immunizing rabbits with a synthetic peptide, Lys-Arg-Ser-Arg-His-Phe, corresponding to the six carboxy-terminal amino acids of the middle T antigen predicted from the nucleotide sequence of polyoma DNA. The antipeptide serum precipitates the polyoma middle T antigen but not the small or large tumor antigens, and precipitation is inhibited in the presence of the peptide. Two cellular proteins, 30,000 and 26,000 daltons, are also precipitated specifically by the antipeptide serum and may have amino acid sequences related to the peptide. Two other cellular proteins, 33,000 and 25,000 daltons, are precipitated only in the presence of the peptide and may associate with it in cell extracts. Antisera directed against synthetic peptides are likely to be important in various ways, including the production of antibodies directed against particular determinants and the recognition of unknown proteins whose genes have been analyzed. (Author abstract) (21 Refs)

30. BK VIRUS-TRANSFORMED INBRED HAMSTER BRAIN CELLS. I. STATUS OF THE VIRAL DNA AND THE ASSOCIATION OF BK VIRUS EARLY ANTIGENS WITH PURIFIED PLASMA MEMBRANES.

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J Virol; 40(1):276-284 1981

Inbred LSH hamster brain cells were transformed in vitro by the GS strain of BK virus (BKV), and transplantable tumors classified as undifferentiated glioblastomas were induced in the syngeneic host. The viral status in the transformed cells, designated LSH-BR-BK, was established. About 46 genome equivalents per cell of viral DNA was detected, with the majority of sequences in a free form. The transformed cells expressed large quantities of tumor (T) antigen as well as surface (S) antigen as demonstrated by indirect immunofluorescence. Sixty-three percent of tumor-bearing hamsters produced high-titer antibodies against T, whereas 3 of 14 (21%) hamsters also produced antibodies against the BKV-specific S antigen. Furthermore, the relatedness of BKV early gene products, including T, S, and tumor-specific transplantation antigen, was established by the production of a rabbit antiserum against highly purified plasma membranes of LSH-BR-BK cells and by the induction of a BKV-specific tumor-specific transplantation antigen response by these plasma membranes in the syngeneic host. (Author abstract) (47 Refs)

31. DETECTION OF MAREK'S DISEASE VIRUS.

Fomina NV
All-Union Res. Inst. Veterinary Sanitation, USSR
Veterinariia; (8):36 1981

To determine the mode of transmission of Marek's disease, 1-day-old leukemia-free chickens were inoculated with Marek's disease virus (MDV). Fluorescence antibody technic showed the presence of MDV antigen first in the liver, feather follicles and dandruff (10 days after inoculation), and then in the thymus (45 days), spleen (52 days), kidneys (60 days), and bursa of Fabricius (67 days). (no Refs) (In RUS)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

32. PHENOTYPIC CHARACTERIZATION IN MICE OF THYMUS TARGET CELLS SUSCEPTIBLE TO PRODUCTIVE INFECTION BY THE RADIATION LEUKEMIA VIRUS.

Boniver J, Decleve A, Honsik C, Leiberman M, Kaplan HS
(c/o Kaplan) Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
JNCI; 67(5):1139-1151 1981

The spread of virus replication was studied by electron microscopy in the thymuses of inbred C57BL/Ka mice after intrathymic inoculation of the radiation leukemia virus (RadLV). The first Type C-budding virus particles appeared in scarce blast cells of the subcapsular zone. Most of these blast cells were 'X-cells,' ie, the thymus lymphoid cells most actively engaged in DNA synthesis. Virus replication spread to the entire cortical blast cell population and, from Day 7 on, to the small

cortical lymphocytes. The first virus-producing cells were derived from a very few target cells (approx 0.001-0.003% of thymocytes) susceptible to RadLV infection. For determination of the phenotypes of these target cells, various thymocyte subpopulations obtained through a battery of cell separation methods were tested for their ability to support the replication of RadLV/VL3 virus in short-term culture. Most of these target cells were sensitive to the lytic effect of hydrocortisone and migrated in the fastest fraction of a 1xG sedimentation gradient, together with the majority of [3H]thymidine-incorporating blast cells. They exhibited an intermediate density and expressed H-2 and Thy 1.2 cell surface antigens, although they were not found preferentially among the high Thy 1.2 population to which most of the cortical blast cells belonged. The sprea d of RadLV within the thymus and the surface phenotype characteristics of target cells indicate that these cells correspond to a thymocyte subset at the earliest stage of thymic lymphopoiesis and may be transitional between the prothymocytes and the subcapsular blast cell population. (Author abstract) (47 Refs)

33. IMMUNOPATHOLOGY OF NATURAL AND EXPERIMENTAL LYMPHOMAS INDUCED BY WILD MOUSE LEUKEMIA VIRUS.

Bryant ML, Scott JL, Pal BK, Estes JD, Gardner MB
(c/o Gardner) Dept. Pathology, Univ. California Sch. Medicine, Davis, CA, 95616
Am J Pathol; 104(3):272-282 1981

Naturally occurring lymphomas of Lake Casitas (LC) wild mice, and the ly.nphomas induced by LC murine leukemia virus (MuLV) in Swiss mice from the National Institutes of Health, displayed remarkably similar gross, microscopic, and functional characteristics. They spared the thymus, arose primarily in the splenic red pulp, became leukemic, and were comprised of stem cells lacking classic T- and B-cell markers. Cytoplasmic and surface Ig were undetectable in 34 of 35 spontaneous LC lymphomas and in aiy of 10 LC MuLV-induced lymphomas in NIH Swiss mice. Assays for Ig secretion, complement (C'3) and Fc receptors, Thy 1.1,2 antigens, Ly 1,2 antigens, and erythroid and myeloid markers were negative on all of the spontaneous and experimental lymphomas. Cell lines were derived from five spontaneous lymphomas of LC mice. Three lines were characterized as null cells, one line as B cells, and one line as macrophages. All cell lines were diploid. The wild mouse spontaneous lymphomas, and lymphomas experimentally induced by LC MuLV in laboratory mice, provide a useful model for childhood acute lymphoblastic leukemia and for study of the early steps of B-lymphocyte differentiation. (Author abstract) (64 Refs)

34. PREVALENCE OF BOVINE LEUKEMIA VIRUS INFECTION IN FLORIDA.

Burridge MJ, Puhr DM, Hennemann JM
Dept. Preventive Medicine, Coll. Veterinary Medicine, Univ. Florida, Box J-136, Gainesville, FL, 32610
J Am Vet Med Assoc; 179(7):704-707 1981

A serologic study was undertaken to determine the prevalence of bovine leukemia virus (BLV) infection in dairy and beef cattle in Florida. Using the agar gel immunodiffusion test with a glycoprotein antigen, 47.8% of 7,768 dairy cattle and 6.7% of 4,9ll beef cattle were found to have antibodies to BLV. The prevalence of BLV antibodies increased significantly (p greater than 0.0001) with increasing age. After data were adjusted for age, prevalence of BLV antibodies was significantly associated with dairy breed (p less than 0.05) but not with species (Bos taurus and B indicus) or sex. (Author abstract) (30 Refs)

35. INDUCTION OF LYMPHOSARCOMA IN SHEEP BY BOVINE LEUKEMIA VIRUS.

Kenyon SJ, Ferrer JF, McFeely RA, Graves DC
(c/o Ferrer) Sch. Veterinary Medicine, Univ. Pennsylvania, New Bolton Center, Ke nnett Square, PA, 19348
JNCI; 67(5):1157-1163 1981

Newborn sheep inoculated with phytohemagglutinin (PHA)-treated short-term cultures of lymphocytes from cattle infected with bovine leukemia virus (BLV) or with a BLV-infected long-term culture of bovine leukemic lymphocytes became persistently infected with BLV. Fifty percent or more of the sheep died with histologically confirmed lymphosarcomas. Cytogenetic studies of representative cases demonstrated that the tumors did not result from the progressive growth of neoplastic lymphocytes in the inoculum but rather from the neoplastic transformation of the recipient's lymphoid cells. Neither BLV infection nor lymphosarcoma was observed in control uninoculated sheep or in sheep given injections of PHA-treated cultures of lymphocytes from BLV-free cows. The virus recovered from the tumorous sheep was indistinguishable from BLV morphologically, antigenically, and biologically, and its reverse transcriptase had the same cation preference and immunologic properties as the BLV enzyme. Persistent BLV infection and lymphosarcoma were also observed in a group of sheep inoculated neonatally with BLV-containing cell-free culture supernatants. These results extend previous observations on the high susceptibility of sheep to BLV infection and provide definitive evidence that BLV is a tumor-inducing virus. (Author abstract) (33 Refs)

36. GENETICS OF SUSCEPTIBILITY TO RADIATION-INDUCED LEUKEMIA. MAPPING OF GENES INVOLVED TO CHROMOSOMES 1, 2, AND 4, AND IMPLICATIONS FOR A VIRAL ETIOLOGY IN THE DISEASE.

Meruelo D, Offer M, Flieger N
Irvington House Inst., New York Univ. Medical Center, New York, NY, 10016
J Exp Med; 154(4):1201-1211 1981

The genetics of susceptibility to radiation-induced leukemia in (A/J x B10)F2 mice were defined and the genes involved were localized. A major locus conferring resistance to fractionated irradiation (Cs-137; 180 rad/wk for 4 wk) induction of leukemia was mapped in chromosome 2 (Ril-1). Loci next to xenotropic murine leukemia virus (MuLV) envelope-related cell-surface antigens (XenCSA) on chromosome 4 (Ril-3) and Pep-3 on chromosome 1 (Ril-2) also influenced susceptibility to the leukemia. Leukemia incidence on day 250 after last irradiation was 86% and 90% in mice lacking the phenotypes Ly-6.2 or Ly-11.2, respectively, on chromosome 2. Effects related to genes linked to Ly-15.2R and Pep-3 loci were less important: the number of phenotype-nonleukemic animals 300 days after irradiation were 29% (phenotype 15.2/15.2) and 15% (Pep-3 phenotype AA). Ril-1 is located in a chromosomal site rich in thymus differentiation-specific loci; a linkage of Ril-1 and Ly-11 suggests that this region of chromosome is not silent to the inductive effects of fractionated irradiation. Tissue-specific activation of endogenous viruses may b e explained by dependency on differentiation-specific steps. (40 Refs)

37. CHARACTERIZATION OF THE BONE MARROW CELL POPULATION EXPRESSING AN AKR MURINE LEUKAEMIA-VIRUS GP71-LIKE ANTIGEN.

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Instituto de Inmunologia y Biologia Microbiana, Velazquez 144, Madrid 6, Spain
Immunology; 44(2):339-345 1981

The murine bone marrow population mainly responsible for the unique competing activity of this lymphoid organ in the competition radioimmunoassay (cRIA) for AKR murine leukemia viruses gp71 has been partially purified and characterized. That population could be distinguished by the following properties: (i) gp71+ cells (cell population expressing the AKR MuLV gp71 antigen) are mainly medium density cells, according to their distribution in the layers of a discontinuous bovine serum albumin (BSA) gradient; (ii) The gp71 positive cells are not mature lymphocytes; (iii) This cell population is found both in the FcR+ and FcR- compartments and is not included in the complement (C') receptor-positive population; and finally, (iv) the gp71+ cells are phagocytic cells and an adherent cell population according to its capacity to adhere to plastic surfaces, nylon wool and Sephadex G-10. (Author abstract) (25 Refs)

38. LEUKEMIA-SARCOMA COMPLEX IN CHICKENS.

Shikov AT, Lutokhin SI, Krasnikov GA, Tsymbal VI, Solov'eva LS
Ukrainian Res. Inst. Experimental Veterinary Medicine, USSR
Veterinariia; (8):42-43 1981

Serological examination of chickens with leukemia showed presence of group specific antigen in 2-51%. Neutralization reaction confirmed that the chicken were carriers of leukemia-sarcoma virus of serological subgroups A, B, and C. (no Refs) (In RUS)

39. RELATION OF BOVINE LEUKOSIS VIRUS PRODUCTION ON CELL GROWTH CYCLE.

Takashima I, Olson C
Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan
Arch Virol; 69(2):141-148 1981

The cell cycle of fetal lamb kidney (FLK) cultures chronically infected with bovine leukosis virus was synchronized by double thymidine block. The synchronized FLK cells were examined for production of BLV antigen and virion release by cytoplasmic immunofluorescence and syncytia forming assay, respectively. The production of BLV antigens was increased during S and G2 phases and was decreased during M and G1 phases. BLV release was associated with the M phase of FLK cells. Short term lymphocyte cultures from BLV infected cattle were treated with hydroxyurea and mitomycin C. The expression of BLV antigen and DNA synthesis of PHA stimulated lymphocytes was inhibited by both drugs. (Author abstract) (21 Refs)

40. EVIDENCE THAT THE SPONTANEOUS BLASTOGENESIS OF LYMPHOCYTES FROM BOVINE LEUKEMIA VIRUS-INFECTED CATTLE IS VIRAL ANTIGEN SPECIFIC.

Thorn RM, Gupta P, Kenyon SJ, Ferrer JF
Univ. Pennsylvania Sch. Veterinary Medicine, New Bolton Center, Kennett Square, PA, 19348
Infect Immun; 34(1):84-89 1981

Cattle lymphocytes cultures for 3 days were found to spontaneously incorporate thymidine (3STI). Under optimal conditions of culture, the median magnitude of 3STI activity in lymphocytes from bovine leukemia virus (BLV)-infected cattle was higher than that of BLV-free cattle, but the ranges of the values overlapped. However, the 3STI activity of most BLV-infected cattle was specifically inhibited by serum containing BLV antibodies, whereas the 3STI activity of BLV-free cattle was not. The 3STI inhibitor copurified with Ig, and its activity could be absorbed with BLV. Rabbit anti-BLV serum inhibited 3STI, but rabbit anti-BLV p25 did not. These results indicate that BLV infection induces or expands a BLV-specific lymphocyte population. Spontaneous blastogenesis may be indicative of an immune response which controls virus spread. (Author abstract) (27 Refs)

41. IMMUNOPROPHYLAXIS OF TRANSPLANTABLE METHYLCHOLANTHRENE-INDUCED MURINE FIBROSARCOMAS BY IMMUNIZATION WITH EMBRYO CELLS EXPRESSING ENDOGENOUS MURINE LEUKEMIA VIRUS ANTIGENS.

Zbar B, Manohar V, Sugimoto T, Ashley MP, Kato Y, Rappaport P
Lab. Immunobiology, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4499-4507 1981

We investigated the nature of a common tumor rejection antigen(s) in chemically induced murine fibrosarcomas. Two methylcholanthrene-induced fibrosarcomas, previously demonstrated to contain a common tumor rejection antigen(s), released infectious ecotropic murine leukemia virus and expressed the murine leukemia virus proteins, a glycoprotein with a mol wt of 70,000 (gp70) and an envelope protein with a mol wt of 15,000. To determine whether an antigen(s) specified by a murine leukemia virus might serve as a common tumor rejection antigen(s), primary cultures of syngeneic embryo cells or cultures of an allogeneic embryo cell line were infected with an endogenous ecotropic murine leukemia virus obtained from one of the cross-reacting fibrosarcomas; expression of infectious virus and/or viral proteins by infected and uninfected embryo cells was monitored and correlated with the results of transplantation protection tests. Uninfected allogeneic embryo cells (SC-1) did not release infectious virus or the viral protein gp70; mice immunized with SC-1 cells did not inhibit tumor growth. Uninfected syngeneic embryo cells did not release infectious virus but did release ug quantities of gp70 into supernatant fluids; mice immunized with uninfected syngeneic cells inhibited tumor growth in two of seven experiments. Virus-infected syngeneic and allogeneic embryo cells released both infectious ecotropic murine leukemia virus and gp70; mice immunized with virus-infected cells inhibited tumor growth in 11 of 11 experiments. Growth of the two cross-reacting fibrosarcomas was inhibited in mice immunized with virus-infected embryo cells. The results indicate that antigens coded for by endogenous murine leukemia virus may function as common tumor rejection antigens on chemically induced murine fibrosarcomas. (Author abstract) (35 Refs)

42. IMMUNOLOGICAL CHARACTERIZATION OF A LOW ONCOGENIC MOUSE MAMMARY TUMOR VIRUS FROM BALB/CNIV MICE.

Vacquier JP, Cardiff RD, Blair PB
(c/o Cardiff) Dept. Pathology, Sch. Medicine, Univ. California Davis, Davis, CA, 95616
J Virol; 40(1):56-64 1981

Antigenic determinants of mouse mammary tumor virus (MuMTV) from the low-mammary-tumor-incidence strain BALB/cNIV were compared by competition radioimmunoas-

say with those of MuMTV's isolated from several high- and low-mammary-tumor-incidence mouse strains, using rabbit hyperimmune sera against BALB/cNIV MuMTV and against MuMTV from the high-mammary-tumor-incidence strain BALB/cfC3H. Using anti-BALB/cfC3H serum in competition radioimmunoassay, BALB/cNIV MuMTV lacked antigenic determinants present on MuMTV's from the BALB/cfC3H, C3H, and GR strains. With anti-BALB/cNIV serum in competition radioimmunoassay, type-specific antigenicity was detected with BALB/cNIV MuMTV. We found class-specific antigenicities on BALB/cNIV MuMTV that were shared with RII and C3Hf MuMTV'S. BALB/cNIV MuMTV was reportedly derived from the C3Hf strain by infection of BALB/c mouse mammary tissue after transplantation into a (BALB/c x C3Hf)F1 hybrid followed by retransplantation into the BALB/c strain. However, BALB/cNIV MuMTV contained type-specific antigens not present on C3Hf MuMTV. The possible origin of these determinants is discussed. (Author abstract) (31 Refs)

43. LOCALIZATION OF MAMMARY TUMORS IN VIVO WITH 131I-LABELED FAB FRAGMENTS OF ANTIBODIES AGAINST MOUSE MAMMARY EPITHELIAL (MME) ANTIGENS.

Wilbanks T, Peterson JA, Miller S, Kaufman L, Ortendahl D, Ceriani RL
(c/o Peterson) Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, 51st and Grove St., Oakland, CA, 94609
Cancer; 48(8):1768-1775 1981

The Fab fragments of antibodies against cell-type-specific surface antigens of mouse mammary epithelial cells (MME-antigens) were used to localize mammary tumors successfully. The radioiodine-labeled anti-MME (Fab) was injected into mice carrying simulated mammary metastases, and after 24 hr the amounts of label per gram of excised tissue was several times greater in the tumor than in liver, brain, lung, or muscle. Kidney showed considerable accumulation of label but this appeared to be nonspecific. Kinetic studies revealed a rapid elimination of labeled Fab in the urine with only 1% of the injected dose remaining in the entire blood pool after 24 hr. With a high-purity germanium camera, mammary tumors were clearly located by the 131I-labeled anti-MME (Fab), and normalization to 99mTc-pertechnetate distribution in the ani mal increased the specificity. The density of 131I-label was fourfold greater over the mammary tumor than over comparable areas of the mouse. No accumulation of 131I-anti-MME (Fab) was observed in nonmammary tumors nor in mammary tumors when labeled nonspecific Fab was used. An analogous system using an antihuman mammary epithelial antiserum is being developed for localization of breast metastases in humans. (Author abstract) (40 Refs)

44. DEMONSTRATION OF ANTIGENIC CROSS-REACTIVITY BETWEEN SIMIAN SARCOMA VIRUS (SSV) AND MASON-PFIZER MONKEY VIRUS (MPMV). BRIEF REPORT.

Micheel B
Central Inst. Cancer Res., Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Virol; 69(2):149-153 1981

The reaction of FITC-labeled simian sarcoma virus (SSV) with anti-SSV p30 antibodies conjugated to Sepharose beads is specifically blocked by incubation with antisera to different Type-C virus p30s and also by anti-MPMV p27 serum. (Author abstract) (14 Refs)

45. BIOLOGICAL PROPERTIES OF ROUS SARCOMA VIRUS ISOLATED FROM TRANSFORMED HAMSTER CELLS.

Cherepantseva EA, Shevliagin VIa
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (4):489-493 1981

The results of comparative evaluation of biological properties of Rous sarcoma virus (RSV) isolated from virogenic hamster 23x cells are reported. RSV isolated from the virogenic cells (RSV-23x) was found to retain the antigenic characteristics of RSV isolated from the original Schmidt-Ruppin cell line (RSV-SR). The RSV-23x induced more effective transformation of mammalian cells than that induced by the RSV-SR. In contrast to the RSV-SR, the RSV-23x was able to reproduce in mammalian cells. (11 Refs) (In RUS)

46. PRODUCTION OF NONINFECTIVE VIRIONS OF ROUS SARCOMA VIRUS BY VIROGENIC HAMSTER CELLS.

Cherepantseva EA, Zakharova LG, Zakhaleva VA, Shevliagin VIa
N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Vopr Virusol; (4):485-488 1981

Production of noninfective virions of Rous sarcoma virus (RSV) was studied in virogenic hamster 23x cells. Electron microscope examination of the virogenic cells showed the presence of two kinds of virions of type C; the majority of the virions had a morphology similar to that of mammalian oncoviruses, and less than 10% of the virions were similar to avian oncoviruses. Virions containing the major internal protein p27 of RSV carried the surface antigenic determinants of hamster oncovirus. (17 Refs) (In RUS)

47. IMMUNOPRECIPITATION OF INTRACISTERNAL A-PARTICLE-ASSOCIATED ANTIGENS FROM PREIMPLANTATION MOUSE EMBRYOS.

Huang TT, Calarco PC
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JNCI; 67(5):1129-1134 1981

Murine intracisternal A-particles (IAP) are endogenous retrovirus particles expr essed in large numbers in certain neoplastic tissues and during early stages of normal preimplantation mouse (outbred ICR) embryogenesis. IAP-associated antigens synthesized by preimplantation mouse embryos were precipitated by a rabbit (New Zealand White) antibody prepared against IAP from murine myeloma 104E. Characterization of the embryo immunoprecipitates with the use of one- and two-dimensional polyacrylamide gel electrophoresis revealed that a group of five proteins was synthesized by two- to eight-cell stages, but only three of these (mol wt of 67,000, 69,000, and 73,000) correlated with the morphologic expression of IAP in embryos. Only the proteins with mol wt of 75,000 and 77,000 were detected in morulae and blastocysts, when embryos were IAP-negative. This is the first biochemical identification of endogenous retrovirus-associated antigens in preimplantation mouse embryos. (Author abstract) (34 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

48. LONG-TERM T-CELL-MEDIATED IMMUNITY TO EPSTEIN-BARR VIRUS.

Rickinson AB, Moss DJ, Wallace LE, Rowe M, Misko IS, Epstein MA, Pope JH
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Cancer Res; 41(11,part1):4216-4221 1981

Experiments are reviewed that support the concept that a virus-induced lymphocyte-detected membrane antigen (LYDMA) elicits a cytotoxic T-cell response that controls persistent Epstein-Barr (EB) virus expression. Specific topics discussed are regression as an in vitro expression of T-cell memory, dependence of regression on cell concentration, EB virus-specific cytotoxic T cells as mediators of regression, LYDMA as the target antigen of effector T cells, reactivation of LYDMA-specific cytotoxicity by stimulation with autologous lymphoblastoid cells, HLA restriction of virus-specific T-cell cytotoxicity, and T-cell memory and the virus carrier state. (49 Refs)

49. CELL-MEDIATED IMMUNE REACTIONS IN THREE PATIENTS WITH MALIGNANT LYMPHOPROLIFERATIVE DISEASES IN REMISSION AND ABNORMALLY HIGH EPSTEIN-BARR VIRUS ANTIBODY TITERS.

Masucci MG, Szigeti R, Ernberg I, Bjorkholm M, Mellstedt H, Henle G, Henle W, Pearson G, Masucci G, Svedmyr E, Johansson B, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4292-4301 1981

Two patients with Hodgkin's disease in remission and one chronic lymphatic leukemia patient with extraordinarily high anti-Epstein-Barr virus (EBV) (viral capsid antigen) antibody titers (greater than 10,000) were selected to study a spectrum of cell-mediated immune responses, including natural killer, interferon-boosted killer, antibody-dependent lymphocytotoxicity, and T-cell-mediated reactions. The purpose was to compare these reactions in patients with immunosuppression and a high EBV load who can hold their EBV-carrying cells under control with the corresponding reactions in patients with EBV-carrying lymphoproliferative disease. In contrast to the latter group, the three patients of the present study showed a less profound and less general suppression of the immune responses. Multiple effector mechanisms probably safeguard against the proliferation of EBV-transformed B-cells. Clinically manifest EBV-carrying lymphoproliferative disease occurs only in very severe immunodeficiencies effecting multiple effectors. (Author abstract) (44 Refs)

50. CELLULAR IMMUNE DEFECTS TO EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS IN YOUNG MALES.

Masucci MG, Szigeti R, Ernberg I, Masucci G, Klein G, Chessels J, Sieff C, Lie S, Glomstein A, Businco L, Henle W, Henle G, Pearson G, Sakamoto K, Purtilo DT
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4284-4291 1981

Three males with the X-linked lymphoproliferative syndrome (XLP) with hypo- or agammaglobulinemia following Epstein-Barr virus (EBV) infection and two males with the chronic mononucleosis syndrome were investigated for immune responses to EBV-determined antigens. Males with XLP showed profound cellular immune defects. Markedly diminished responses of natural killer cell and interferon-activated killer cell activities and impaired WBC migration inhibition responses to phytohemagglutinin were determined in patients with XLP. The two patients with chronic mononucleosis showed less severe defects. All patients showed partial or complete impairment of their EBV-specific immune responses as measured by WBC migration inhibition. EBV-specific antibodies were markedly diminished against EBV-associated nuclear antigen, early antigen, and viral capsid antigen in males with XLP. In contrast, patients with chronic mononucleosis had elevated antibodies to most EBV-specific antigens. Individuals with life-threatening EBV-induced lymphoproliferative disorders may exhibit multiple defective immune mechanisms against the virus. (Author abstract) (44 Refs)

51. EPSTEIN-BARR VIRUS-SPECIFIC SEROLOGY IN IMMUNOLOGICALLY COMPROMISED INDIVIDUALS.

Henle W, Henle G
Joseph Stokes, Jr., Res. Inst., Children's Hosp. of Philadelphia, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Cancer Res; 41(11,part1):4222-4225 1981

Since B-lymphocytes are targets and a continuing habitat of Epstein-Barr virus (EBV) and the cell-mediated immune system becomes secondarily involved, one may anticipate that primary and persistent EBV infections in immunologically compromised individuals take unusual courses. Depending on the immunological defect, the clinical, hematological, and serological responses to primary EBV infections may be more or less pronounced than in immunologically competent patients. Infectious mononucleosis has per se an immunosuppressive effect which may enhance a preexisting immune defect. The persistent latent viral carrier state which regularly ensues after the primary EBV infection may become decontrolled by immunosuppressive diseases or therapy, leading rarely to illnesses referable to the virus but often to increases in the titers of antibodies to viral capsid and early antigens and/or declines in the antibody titer to EBV-associated nuclear antigen. Absence or dysfunction of different WBC subpopulations may account for the differential changes in antibody patterns. (Author abstract) (42 Refs)

52. T-CELL RESPONSE TO B-CELLS AND EPSTEIN-BARR VIRUS ANTIGENS IN INFECTIOUS MONONUCLEOSIS.

Klein E, Ernberg I, Masucci MG, Szigeti R, Wu YT, Masucci G, Svedmyr E
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Cancer Res; 41(11,part1):4210-4215 1981

After Epstein-Barr virus (EBV) infection in vivo, B-cells with latent virus infection persist indefinitely through life. These cells grow in vitro on explantation and can be established as immortal B-cell lines. To reconcile the unlimited growth potential in vitro with the maintenance of a low proportion of B-cells infected by EBV in vivo, a strict in vivo control mechanism has to be postulated. Certain aspects of this control are apparent when the primary infection is followed by infectious mononucleosis. This is characterized by lymphocytosis and the presence of activated T-cells. The T-cell proliferation is probably the manifestation of the immune response against EBV antigens. However, the reaction of T-cells upon encounter of B-blasts is also likely to contribute to the events. At present, it is difficult to detect an EBV-specific component

in the action of the T-cells in the acute phase of mononucleosis exerted on B-cells. However, for the clinical course of the disease the activation of T-cells is important. The activated T-cells may control and also eliminate the B-cells infected by EBV. In addition to the immunity which develops during the disease, the immunoregulatory mechanism is likely to have a role in the inhibition of B-cell proliferation. (Author abstract) (52 Refs)

53. THE CYTOTOXIC EFFECT OF LYMPHOCYTES FROM PATIENTS WITH NASOPHARYNGEAL CANCER (NPC) AGAINST A NPC EPITHELIOID CELL LINE..

Lin Y, Zhao W, Zeng Y, Liu C, Hu G

Tumor Unit, Inst. Virology, Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Zhongliu Zazhi; 3(1):1-4 1981

Using a cell line derived from esophageal carcinoma (ECa109), the cytotoxic effects of lymphocytes obtained from NPC as well as other malignant and nonmalignant diseases were studied in vitro against an NPC epithelial cell line (CNE). Of 224 subjects tested, lymphocytes from 827. Of the NPC patients before radiotherapy exhibited cytotoxicity against CNE cells. However, lymphocytes from only 10% to 18%. Of other malignant and nonmalignant diseases showed cytotoxicity against CNE while lymphocytes from normal individuals showed only 6% cytotoxicity rate. (p less than 0.0001). Only 4% of NPC patients had cytotoxic lymphocytes against ECa109. The cytotoxic effects of lymphocytes from NPC patients were related to radiotherapy and clinical course, with a decrease from 82% to 23% cytotoxicity rate within 3 mo after radiotherapy and subsequent increase to 70% after 3 mo. The rate in patients who had metastasis or recurrence of disease after radiotherapy was 13%. It was also found that the lymphocyte cytotoxicity of NPC patients was related to EBV antibodies (VCA-IGA) reactivity. (14 Refs) (In CHI)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

54. EFFECTS OF HYDROCORTISONE ON THE SYNTHESIS OF EPSTEIN-BARR VIRUS ANTIGENS IN P3HR-1 CELLS.

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Dept. Experimental Virology, Inst. Sera and Vaccines, 181 03 Prague, Czechoslovakia

Acta Virol (Praha); 25(3):163-166 1981

Hydrocortisone was capable of enhancing the synthesis of Epstein-Barr virus antigens in producer P3HR-1 cells which had been induced with a 24-hr pulse of 5-iodo-2-deoxyuridine. The effect of hydrocortisone was time dependent, suggesting that an early step in the induction process, and not the antigen synthesis itself, was influenced by the drug. (Author abstract) (10 Refs)

55. STEROIDS INHIBIT TUMOR PROMOTING AGENT INDUCED EPSTEIN-BARR VIRUS EARLY ANTIGENS IN RAJI CELLS.

Sundar SK, Ablashi DV, Armstrong GR, Zipkin M, Faggioni A, Levine PH

Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205

Int J Cancer; 28(4):503-507 1981

Four steroids and one protease inhibitor were evaluated for their effects on 12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced and Epstein-Barr virus-induced early antigens (EBV-EA) in Raji cells. Continuous treatment with dexamethasone, prednisolone, hydrocortisone and cortisone inhibited TPA-induced EBV-EA to varying degrees, but the protease inhibitor N-alpha-p-tosyl L-lysine chloromethyl ketone-HCl (TLCK) had no significant effect. None of the agents tested inhibited EBV-induced EA. In addition, the effect of the steroids was reversible since the removal of these agents resulted in recovery of the percentage of EBV-EA-positive cells in TPA-treated cultures. These results were in agreement with the in vivo experiments of other investigators, who demonstrated inhibition of tumor promotion with steroids. Since TLCK failed to inhibit TPA-induced EA, it is unlikely that induction of EA by TPA is the result of production of proteases. (Author abstract) (36 Refs)

56. ENHANCEMENT OF ANTIBODY-COMPLEMENT CYTOTOXICITY AGAINST VIRUS-TRANSFORMED HAMSTER PARA-7 CELLS TREATED WITH HEAT AND MICROWAVE RADIATION.

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Radiat Res; 88(1):96-107 1981

Effects of both water-bath heating and microwave exposure on the sensitivity of Simian virus(SV) 40-transformed hamster cells (PARA 7) to cytotoxic effects of antibody and complement are reported. The PARA 7 tumor cell line was obtained from transformation of LSH hamster embryo fibroblasts into fibrosarcoma. Three ml PARA-7 cell suspensions were harvested, resuspended and irradiated in liquid scintillation vials with microwaves (100 milliWatts(Ws)/square cm; 105 Ws/kg). Antibody-complement (Ab-C) cytotoxicity was assayed with 51Cr release and colony-formation (CF). Progressive loss of cell viability was observed when cells were heated for 30 min or more at 37-43 C. The heated cells showed increased sensitivity to Ab-C cytotoxicity when antibodies directed against whole cell membranes or cell membrane-associated SV40 tumor-specific antigen was used. PARA 7 cells exposed to microwaves under the same variable temperatures show similar loss of cell viability and increased sensitivity to Ab-C cytotoxicity, but under constant temperature (37 C), based on both the 51Cr release and CF assays, exposure to microwaves did not result in significant loss in viabilty or sensitivity to Ab-C. The results suggested that the effects of microwave exposure are thermal in origin. The data also showed that the loss of cell viability and sensitization to Ab-C cytotoxicity following water-bath heating or microwave exposure are not significantly different if the temperature is held constant. (28 Refs)

OTHER RELATED STUDIES

57. PREVENTION OF TUMORS IN RATS BY CROSS-PROTECTIVE IMMUNIZATION.

Fish DC, Bare AL, Djurickovic DB, Huebner RJ
NIH Intramural Res. Program, NCI Frederick Cancer Res. Center (FCRC), Frederick, MD, 21701
JNCI; 67(5):1041-1051 1981

F344 inbred rats were repeatedly immunized (days 0, 28, and 42) with normal syngeneic or allogeneic rat tissues or transplantable syngeneic or allogeneic rat tumors (some of which were virus producing). Immunized rats were challenged by sc injection of 10(5) or 10(6) syngeneic rat tumor cells from either of two different tumor lines. Successful cross-protective immunization prevented tumor development in rats that were challenged at 100-1,000x the 50% tumor dose. The protection was essentially lifelong and complete in that no tumors appeared up to 200 days post challenge in some experiments. To be successful, the tumor cell vaccines had to express a complement-fixing, cross-reacting antigen detected with sera from rats bearing any of several different tumors and to be able to induce a spontaneously regressing tumor in the host. (Author abstract) (34 Refs)

58. HUMAN LIVER NUCLEOLAR ANTIGENS.

Busch RK, Busch H
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Proc Soc Exp Biol Med; 168(1):125-130 1981

Normal human liver nucleoli were used to immunize rabbits and the resultant antibodies were used to study antigens in human liver and other tissues. Immunofluorescence studies with the antibodies to human liver nucleoli, showed nucleoli as bright fluorescent organelles against a less fluorescent nuclear background. In most tissue sections, a limited number of fluorescent nucleoli were observed. Nuclear membrane fluorescence was frequently observed. In HeLa cells, the localization of fluorescence was less restricted. Nucleolonemal and nuclear network fluorescence was visible. In the placental sections, few nucleoli were found and more background fluorescence was noted. Immunodiffusion analysis revealed two immunoprecipitin bands which appeared to be liver specific. Other immunoprecipitin bands were common to liver, placenta, and HeLa nuclear extracts. Rocket immunoelectrophoresis revealed two liver-specific antigens (L1 and L4), one migrating to the cathode and the other to the anode. Thus liver nucleolar-specific antigens, not found in Hela placental cells, were identified. It was suggested that since a neoplasm may result from a loss of normal protein, information on normal human liver nucleolar and nuclear antigens may aid in the detection of specific proteins lost in neoplasia. (16 Refs)

59. IN VITRO PRODUCTION OF HUMAN ANTIBODY TO A TUMOUR-ASSOCIATED FOETAL ANTIGEN.

Irie RF, Jones PC, Morton DL, Sidell N
Div. Oncology, Univ. California Sch. Medicine, 54-140 CHS, Los Angeles, CA, 90024
Br J Cancer; 44(2):262-266 1981

After the establishment of lymphoblastoid cell lines that synthesize antibody directed against a human tumor-associated fetal antigen designated as oncofetal antigen-I (OFA-I), a method is described for the production of IgM anti-OFA-I in vitro. Ten serum samples containing high levels of anti-OFA-I were identified and viably frozen peripheral-blood lymphocytes (PBL) from the same patients were transformed by Epstein-Barr virus (EBV). Patients included five given adjuvant immunotherapy with an OFA-I+ tumor-cell vaccine (TCV), three treated with BCG, and two treated only by surgical excision. Anti-OFA-I levels in the spent medium were monitored by immune-adherence using the OFA-I+ melanoma cell line UCLA-SO-M14 (M14), as the target cell. Two of the EBV-infected cultures (ES from the TCV group and CD from the surgery only group) produced detectable antibody to M14 cells by day 6. By day 9, culture DV (BCG group) became positive. The CD culture was positive only for 9 days, while ES (obtained from the patient with the highest anti-OFA-I titer) ceased growth after 3 wk. The supernatants displayed no reactivity against a control lymphoblastoid cell line autologous to the M14 donor. The DV lymphoblasts continued to produce increasing titers of anti-M-14 antibody until day 42, with gradual decrease by day 60 and became negative on day 66. None of the other 7 PBL cultures became positive to M14. Further studies determined that the antibody exhibited specific reactivity to an antigen associated with human cancer. No antibody reactivity in the DV culture medium was detected to a number of target cells tested. Assessment of the immunoglobulin class indicated the anti-OFA-I was limited to the IgM class. The DV spent medium was cytotoxic in the presence of either rabbit or human complement. (21 Refs)

60. DISTRIBUTION OF COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN IN NONHEMATOPOIETIC TISSUES.

Metzgar RS, Borowitz MJ, Jones NH, Dowell BL
Dept. Microbiology, Duke Univ. Medical Center, Durham, NC, 27710
J Exp Med; 154(4):1249-1254 1981

The presence of common acute lymphoblastic leukemia antigen (CALLA) in certain cell types of nonhematopoietic adult and fetal tissues was examined by immunoperoxidase staining with the J-5 monoclonal antibody. Portions of normal tissues were removed during the course of surgery from patients with leukemia or lymphoma and a 20-wk-old fetus was obtained from a prostaglandin-induced abortion. Compared to control ascites fluid from BALB/c mice injected ip with the P3 x 63Ag8 myeloma cell line (P3), no significant staining was found in the fetal heart, liver, lung, pancreas, salivary gland, spleen, or thymus, or in the adult skeletal muscle, spleen, tonsil, salivary gland, small intestine, or colon. However, significant staining was observed in adult kidney, fetal kidney, fetal small intestine, and the myoepithelial cell layer of adult breast. In particular, the J-5 antigen was present on proximal tubules and glomeruli of the kidney. The glomerular staining may have been on the podocyte and not the basement membrane. CALLA was shown to migrate as a 90,000 mol wt antigen rather than the 98,000-100,000 mol wt antigen noted on CALLA-positive tissue culture cell lines. The determinant defined by the J-5 monoclonal antibody may be neither lymphoid cell-specific differentiation antigen nor leukemia-specific antigen. (20 Refs)

61. HETEROGENICITY AND SPECIFICITY OF TUMOR ASSOCIATED ANTIGENS (TAA) AND FETAL ANTIGENS (FA) AS DETECTED BY 51CR-LAI TEST AND EM TEST IN MOUSE SARCOMA.

Werner H, Schulze HA
Res. Unit Immunology, Wilhelm Pieck Univ., DDR-2500 Rostock, E. Germany
Arch Geschwulstforsch; 51(6):481-484 1981

Murine tumor associated antigens (TAA) and fetal antigens (FA) were characterized by immunological methods. Antigens were obtained from fetuses at the 10th-14th day of gestation and chemically-induced sarcomas from CBA, B10D2 mice. Soluble extracts were prepared and separated using the Ultrogel AcA 34. Single antigen fractions were incubated with spleen cells from pregnant or tumor-bearing mice. Response was measured by 51Cr lymphocyte adherence inhibition (LAI)and electrophoretic mobility (EMT) tests. Different antigen activities were found for three antigen fractions: P1 (mol wt 200,000-250,000), P2 (mol wt 120,000-160,000), and P3 (mol wt 50,000-60,000). EMT correlated with LAI for P2, but not for P1 or P3. LAI detected some specific components of P1, but failed to detect a common tumor type specificity in P3. Pregnancy specificity was localized in the P2 fraction of FA. (6 Refs)

62. CORRELATION OF GLYCOSPHINGOLIPIDS AND SIALIC ACID IN YAC-1 LYMPHOMA VARIANTS WITH THEIR SENSITIVITY TO NATURAL KILLER-CELL-MEDIATED LYSIS.

Yogeeswaran G, Gronberg A, Hansson M, Dalianis T, Kiessling R, Welsh RM
(c/o Welsh) Dept. Pathology, Univ. Massachusetts, Worcester, MA, 01605
Int J Cancer; 28(4):517-526 1981

Sialoglycoconjugates and glycosphingolipids were quantitated in a series of variants derived from the YAC-1 lymphoma, known to be highly sensitive to natural killer (NK)-cell-mediated lysis. The variants, which had widely diverging sensitivities to NK cells, were obtained by a number of methods, including selection in the presence of NK cells, antibody to H-2, or antibody to the murine leukemia-virus-induced antigen, and by fusion of sensitive cells with an NK-resistant cell line, A9HT. The sensitivities of these cells to NK-cell-mediated lysis did not correlate with their sensitivities to anti-H-2a cytotoxic T cells. While no correlation could be made between the NK-sensitivity of these variants and their total cellular sialic acid, a statistically significant inverse correlation was observed between the levels of percentage neuraminidase releasable surface sialic acid of total labeled sialyl components and sensitivity to NK cells. This correlation with cell surface sialic acid was observed with either endogenous or lymphocytic choriomeningitis virus-induced activated NK cells as effectors. Neuraminidase treatment of insensitive target cells caused a moderate increase in sensitivity but failed to render the resistant targets as sensitive as YAC-1. Analysis of glycosphingolipids among the variants revealed a strong positive correlation between the total cell neutral glycolipid with chromatographic migration of asialo-GM2 and sensitivity to endogenous or activated NK-cell-mediated lysis. Significant correlations were not found with any other neutral glycolipids. However, ganglioside homologues with chromatographic mobility of GM1, GD1a, GD1b, and GT also showed a positive correlation with both endogenous and activated NK-cell-mediated lysis. The ratio of asialo-GM2 to GM2 had a highly significant positive correlation with sensitivity. These correlative results suggest that asialo-GM2 and certain gangliosides could be involved in binding or lytic events in NK cell:target cell interactions, and that high levels of sialic acid and sialylation on the cell surface may inhibit and/or modify such interactions Further studies with these YAC variants should be useful for examining the biochemical basis of target cell-effector cell interactions in the NK system. (Author abstract) (41 Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. REGULATION OF HUMAN T-CELL PROLIFERATION: T-CELL GROWTH FACTOR AND ISOLATION OF A NEW CLASS OF TYPE-C RETROVIRUSES FROM HUMAN T-CELLS.

Gallo RC, Poiesz BJ, Ruscetti FW
NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:502-514 1981

Recent results with human T-cell growth factor (TCGF), the various T cell systems, and the isolation of a new type-C retrovirus released from growing T-cells from some of these T-cell neoplasias are summarized. Unlike normal T-cells, neoplas-

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tic mature T-cells respond directly to TCGF without prior lectin or antigen in vitro activation. Transformed T-cell lines exhibit phenotypic characteristics consistent with the neoplastic cells of their disease of origin. A new retrovirus, human T-cell lymphoma-leukemia vir us (HTLV) was isolated from fresh and cultured cells from two patients, each with a variant of a cutaneous T-cell lymphoma. Further studies showed that HTLV was not significantly related to any known animal retrovirus, is not an endogenous (genetically transmitted) virus of man, and at present is only associated with fresh or cultured T-cells from patients with the T-cell neoplasia. The results suggest that HTLV infected some mature T-cells of some people and may be involved in some neoplasias involving these cells. (33 Refs)

2. B-LYMPHOTROPIC PAPOVAVIRUS (LPV) -- INFECTIONS OF MAN?

Brade L, Gissman L, Mueller-Lantzsch N, Zur Hausen H
Institut fur Virologie, Zentrum fur Hygiene, Hermann-Herderstrasse 11, 7800 Frieburg i. Br., W. Germany
Haematol Blood Transfus; 26:204-206 1981

Papovavirus-like particles that were first observed in supernatants of Epstein-Barr virus (EBV)-transformed lymphoblastoid cell lines from African green monkeys (AGM) were isolated and characterized. The host range for this virus consisted only of B-lymphoblasts from AGM and from one EBV-negative human cell line (line BJA-B), giving this virus the tentative designation lymphotropic papovavirus (LPV). LPV DNA is slightly smaller than SV40 DNA, weighing 3.2 x 10(6) daltons; it yields very different fragments than does SV40 DNA when these two DNA species are digested with Hae III enzyme. After greater than 1 yr of continuous passage in BJA-B cells, the LPV DNA became very heterogenous when examined by gel electrophoresis, apparently due to the accumulation of defective DNA molecules. LPV differs antigenically from all papovaviruses characterized so far. When human sera were tested for antibody to LPV, only about 10% of individuals less than 29 yr old were positive, whereas approx 30% of individuals greater than 30 yr old were positive. No disease-specific reactivity for LPV has so far been demonstrated, although some correlations between the presence of LPV antibodies in the sera and symptoms involving the lymphatic system have been noted. LPV may represent a new subgroup of papovaviruses that could have a role in proliferative diseases of the lymphatic system. (9 Refs)

3. HEPATOCELLULAR CARCINOMA AND HEPATITIS-B-VIRUS: MORE ON THEIR RELATIONSHIP (MEETING ABSTRACT).

de Franchis R, Primignani M, Vecchi M, Zannier PM, Colombo M, Colucci G, Tommasini M
Clinica Medica III, University of Milano, Milan, Italy
Gastroenterology; 80(5,part2):1329 1981

To evaluate the strength of the association of Hepatocellular Carcinoma (HCC) with current or past Hepatitis-B-Virus (HBV) infection, serum HBV markers were studied in three groups of age and sex-matched patients: (a) 33 subjects with HCC, b) 33 patients with chronic active hepatitis and c) 33 hospitalized controls. Sera were tested for hepatitis B surface antigen (HBsAg), anti-HBs, an ti-HBc, anti-HBc titre, HBeAg and anti-HBe by radioimmunoassay by means of commercially available kits (Abbott). The overall exposure rate to HBV (positivity for any one marker) was 94% in HCC, 85% in CAH, and 57% in controls. The prevalence of HBsAg was 36%, 12% and 9% in the three groups respectively. Prevalence of anti-HBs was much lower in HCC (3%) than in CAH (48%) and in controls (39%). Conversely, the prevalence of isolated anti-HBc positivity was 54% in HCC, 24% in CAH and 9% in controls. Serologic evidence of current HBV infection (HBsAg positivity, high-titre anti-HBc or HBeAg positivity) was more common in HCC (54%) than in CAH (18%) and controls (9%). The overall exposure rate to HBV is similar in HCC and CAH. However, serological evidence of continuing viral replication is much more common in the former group. A defective clearance of HBV in HCC is a possible explanation of the phenomenon. (no Refs)

4. EPIDEMIOLOGIC, ETIOLOGIC AND IMMUNOLOGIC ASPECTS OF NASOPHARYNGEAL CARCINOMA (NPC).

Gastpar H, Wilmes E, Wolf H
Univ. ENT Clinic, Pettenkoferstr. 8a, D-8000 Munich 2, W. Germany
J Med; 12(4):257-284 1981

Epidemiologic studies indicate that mainland Chinese, especially those living in the South-East provinces, and overseas Chinese have the highest incidence of nasopharyngeal carcinoma (NPC) in the world. Most of the NPCs in this high-risk population are squamous cell carcinomas. Genetic and environmental factors implicated in NPC etiology are discussed, including HLA profiles, a putative second locus antigen (Sin-2) found in high-risk Chinese, environmental carcinogens, and vitamin A deficiency. Evidence for the role of Epstein-Barr virus (EBV) in NPC is presented. NPC patients have high antibody titers against all EBV antigens, and viral DNA has been detected in NPC epithelial cells. Early EBV infections may increase the likelihood of lymphocyte EBV induction and activation by environmental factors. (110 Refs)

5. ADULT T-CELL LEUKEMIA: ANTIGEN IN AN ATL CELL LINE AND DETECTION OF ANTIBODIES TO THE ANTIGEN IN HUMAN SERA.

Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, Shirakawa S, Miyoshi I
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Proc Natl Acad Sci USA; 78(10):6476-6480 1981

Indirect immunofluorescence of certain human sera demonstrated an antigen(s) in the cytoplasm of 1-5% of the cells of a T-cell line, MT-1, from a patient with adult T-cell leukemia (ATL), which is endemic in southwestern Japan. The antigen was not detected in other human lymphoid cell lines, including six T-cell lines, seven B-cell lines, and four non-T non-B cell lines. The antigen did not show cross antigenicity with that of herpesviruses, including Epstein-Barr virus, herpes simplex virus, cytomegalovirus, varicella-zoster virus, herpesvirus saimiri, and Marek disease virus. The proportion of antigen-b earing cells was increased by a factor of approx five on culture in the presence of 5-iodo-2'-deoxyuridine. Antibodies against the antigen in MT-1 cells were found in all 44 patients with ATL examined and in 32 of 40 patients with malignant T-cell lymphomas (most of them had diseases similar to ATL except that leukemic cells were not found in the peripheral blood). The antibodies were also detected in 26% of the healthy adults examined from ATL-endemic areas but in only a few of those examined from ATL-non-endemic areas. On electron microscopy, extracellular Type C virus particles were detected in pelleted MT-1 cells cultured in the presence of 5-iodo-2'-deoxyuridine. (Author abstract) (26 Refs)

6. AN AUTOPSY STUDY OF HEPATOCELLULAR CARCINOMA IN HONG KONG.

Ho J, Wu PC, Kung TM
Pathology Dept., Univ. Hong Kong, Queen Mary Hosp. Compound, Hong Kong, Hong Kong
Pathology; 13(3):409-416 1981

Two hundred and eighty-seven autopsy cases of hepatocellular carcinoma (HCC) in Chinese were reviewed. The analyses included histological study of the tumor and of the non-cancerous liver tissue, the cause of death and metastases. Bleeding of esophageal varices was most frequent but rupture of tumor less common in cases associated with cirrhosis than in those without cirrhosis. There was a significantly higher incidence of bilobar involvement by tumor in the clear cell type of HCC and in cases unassociated with cirrhosis compared to other histological types of HCC and HCC with cirrhosis, possibly because of longer survival of the former groups. A strong association was found between cirrhosis and hepatic fibrosis with HCC and hepatitis B surface antigen (HBsAg), suggesting an oncogenic effect of chronic persistent hepatitis B virus (HBV) infection on hepatocytes. (Author abstract) (16 Refs)

7. LIVER CELL DYSPLASIA IN ASSOCIATION WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS AND HEPATITIS B SURFACE ANTIGEN IN HONG KONG.

Ho JC, Wu PC, Mak TK
Dept. Pathology, Univ. Hong Kong, Hong Kong, China
Int J Cancer; 28(5):571-574 1981

Liver-cell dysplasia was identified in 60% of 558 cases of cirrhosis with and without hepatocellular carcinoma (HCC) in Chinese coming to necropsy in Hong Kong from 1963 to 1978. A significant correlation was found between liver-cell dysplasia and the identification of hepatitis B surface antigen (HBsAg) in the livers, suggesting that dysplasia may be causally related to hepatitis B virus (HBV). Applying Bayes' theorem to our series of male deaths, we calculated that for Chinese male non-cirrhotics showing liver-cell dysplasia at necropsy, compared with male non-cirrhotics showing no liver-cell dysplasia, the approximate risk factor for HCC is 13:1, whereas for male cirrhotics with liver-cell dysplasia, compared with male cirrhotics without liver cell dysplasia, the risk factor for HCC is approx 2:1. In the presence of dysplasia, the risk for HCC is increased two-fold in males who are also HBsAg-positive. Thus, the presence of liver-cell dysplasia in cirrhotic or non-cirrhotic livers accompanies a significantly higher risk of developing HCC, especially in the presence of HBsAg. (Author abstract) (10 Refs)

8. EPISOMAL SIMIAN VIRUS 40 GENOMES IN HUMAN BRAIN TUMORS.

Krieg P, Amtmann E, Jonas D, Fischer H, Zang K, Sauer G
(c/o Sauer) Inst. Virus Res., German Cancer Res. Center, 6900 Heidelberg, W. Germany
Proc Natl Acad Sci USA; 78(10):6446-6450 1981

Eight out of 35 human intracranial tumors were shown by restriction enzyme analysis to contain unintegrated simian virus 40 (SV40) DNA molecules. The relative amount of viral DNA was estimated to be the equivalent of one viral genome within every 10th to 20th cell. No infectious virus was detected in tissue cultures established from the tumors. From only one tumor was it possibie to rescue, by cell fusion, infectious SV40 displaying wild-type properties. In those cases that permitted a more detailed analysis, the restriction enzyme cleavage patterns appeared to correspond to the wild-type patterns with one exception, in which the SV40 episomes displayed a deletion of approx 70 base pairs close to the origin of DNA replication. From one tumor, the SV40 genomes were transferred into permissive CV-1 monkey cells by transfection with the total tumor DNA. Despite their persistence as episomes no infectious virus was produced. Furthermore, no viral antigens were detectable, although the SV40 messengers for the small and the large tumor antigens were present. These cells had, however, acquired the ability to form colonies in lower concentrations of serum. Thus this report provides, by restriction enzyme analysis, direct evidence for the presence of SV40 DNA in human tumors. (Author abstract) (34 Refs)

9. EVIDENCE FOR PAPILLOMAVIRUS GENUS-SPECIFIC ANTIGENS AND DNA IN LARYNGEAL PAPILLOMA.

Lancaster WD, Jenson AB
Dept. Surgery, Univ. Hosp., 2065 Adelbert Road, Cleveland, OH, 44106
Intervirology; 15(4):204-212 1981

Four juvenile laryngeal papillomas (JLPs) were examined for papillomavirus genus-specific structural antigens and polynucleotide sequences employing reagents derived from bovine papillomavirus Type 1 (BPV-1). Three of four JLPs contained intranuclear antigens in the granular layer of differentiating epithelial cells of formalin-fixed, paraffin-embedded papillomas assayed by the peroxidase-antiperoxidase reaction using an antiserum prepared against purified detergent-disrupted BPV-1. Examination of these JLPs for viral sequences indicated two tumor DNA preparations contained polynucleotide sequences which hybridized to an in vitro labeled BPV-1 DNA probe under nonstringent conditions. These sequences were detectable after gel electrophoresis and immobilization of restriction-endonuclease-digested JLP DNAs onto nitrocellulose membranes. Specific hybridization of probe to digested JLP DNA was visualized as bands in autoradiograms coincidental with open circular and linearized papillomavirus DNA. Hybridization was extensively reduced when JLP DNA preparations were prehybridized to an unlabeled papillomavirus DNA heterologous to the probe. These results provide direct evidence for the association of a papillomavirus in JLP. (Author abstract) (32 Refs)

10. PREVALENCE OF ANTIBODIES TO HEPATITIS A ANTIGEN IN SERA FROM PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES.

McFarlane ES, Embil JA
Dept. Microbiology, Dalhousie Univ., Halifax, Nova Scotia, B3H 4H7, Canada
J Med Virol; 8(1):49-53 1981

Prevalence of antibodies to hepatitis A (anti-HA) was studied by radioimmunoassay in 130 patients with hematological malignancies. Types of malignancies included Hodgkin's disease (31 patients), lymphosarcoma (31), chronic lymphatic leukemia (13), acute lymphoblastic leukemia (11), reticulum cell sarcoma (10), and other types (34). Of the patients studied, 44% of those 4-26 yr old, 70% of those 27-50 yr old, and 83% of those 51-76 yr old were positive. Older patients (51-76 yr old) with hematological malignancies had a significantly higher prevalence of anti-HA than did volunteer Red Cross donors (78.9% vs 59.8% for rural dwellers, $P = 0.01$ and 100% vs 82.6% for urban dwellers, $P = 0.05$). Six patients seroconverted from anti-HA-negative to anti-HA-positive 10-39 mo after initial visit to the clinic. (17 Refs)

11. A GEOGRAPHICAL STUDY OF ANTIBODIES TO MEMBRANE ANTIGENS OF HSV-2-INFECTED CELLS AND HSV-2-SPECIFIC ANTIBODIES IN PATIENTS WITH CERVICAL CANCER.

Mendis LN, Best JM, Senarath L, Chiphangwi J, Vestergaard BF, Banatvala JE
Dept. Microbiology, Faculty of Medicine, Post Office Box 271, Kynsey Road, Colombo 8, Sri Lanka
Int J Cancer; 28(5):535-542 1981

Sera were obtained from patients with squamous carcinoma of the cervix from Great Britain (29), Sri Lanka (32), Malawi (27) and Sudan (27), and from controls from all countries except Sudan. Controls were matched for ethnic origin, age and social class. Sera were tested by indirect immunofluorescence (IF) for IgG and IgA antibodies to membrane antigens (MA) and IgA antibodies to VCA of HSV-2 infected cells. Compared with controls, IgA antibodies to MA (IgA anti-MA) were detected more frequently and at higher titers in all groups of patients. However, there was no significant difference in prevalence of these antibodies at titers greater than or equal to 1:4 between Malawian patients and controls, although a significantly higher proportion of patients had IgA anti-MA titers of greater than or equal to 1:16. In contrast, IgA anti-VCA did not distinguish patients from controls. More than 90% of both patients and controls from all countries had IgG antibodies to MA (IgA anti-MA). Malawian patients had a significantly higher geometric mean titer (GMT) of IgG anti-MA than controls and both patients and controls had significantly higher GMTs than their counterparts from other countries. The variation between herpes IgG anti-MA titers in subjects from different countries did not reflect differences in serum Ig levels and similar variations in titer were not seen in rubella and measles HAI titers. Among the patients there was a geographical variation in the prevalence of HSV-2 specific antibodies detected by ELISA, which varied from 52% among British and Sudanese patients to 73% among Malawian patients. Even when adjustment was made for possible false negative results, there were between 10 and 31% patients without HSV-2-specific antibodies, although only 2 of 103 (1.9%) patients had neither HSV-1 nor HSV-2 antibodies. The association of HSV-2 with cervical carcinoma appeared to vary with age. (Author abstract) (52 Refs)

12. PREVALENCE OF HEPATITIS B SURFACE ANTIGEN (HBSAG) AND ANTIBODY (ANTIHBS) IN PRIMARY LIVER CANCER DETERMINED BY RADIOIMMUNOASSAY AND PASSIVE HEMAGGLUTINATION TECHNIQUES (MEETING ABSTRACT).

Paulin RH, Piquet J, Seck SM, Tartarin O
No affiliation given
Eur J Nucl Med; 6:A23 1981

In previous studies from Senegal, HBsAg was found by agar gel diffusion or counterelectrophoresis techniques in serum of 39-42% of patients with primary liver cancer (PLC) as compared to 9-11% of controls. We report herein an investigation of the prevalence of HBsAg and antiHBs, utilizing in comparative trial the most sensitive of current assay methods. The study related to 164 subjects of black race from West Africa living in Senegal: 82 PLC matched with 82 age/sex hospitalized controls. HBsAg was determined by the Ausria II 125 test and antiHBs by the Ausab system: two solid phase radioimmunoassay procedures. The sera were also tested by passive hemagglutination assay (PHA). The serologic manifestations of HB are usual for PLC in Senegal. For each group the HBsAg and antiHBs frequencies were significantly higher with radioimmunoassay (RIA) than with PHA. The most important difference is registered for the controls. So, in order to value the prevalence RIA was the most sensitive procedure. Consequently, in PLC 71% against 17% in the controls very high level of contamination with the Australian antigen was observed a low immune response to surface antigen of the HB virus: presence of antibodies in 22% of the cases only among the PLC against 58% for the controls. This pattern found of the surface indicators in PLC fits in most cases with the unfavorable evolution of chronic hepatitis: persistance of HBsAg and no appearance of antiHBs antibodies. (2 Refs)

13. IMMUNOPATHOLOGY OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME.

Purtilo DT
Dept. Pathology, Univ. Massachusetts Medical Center, Worcester, MA, 01605
Haematol Blood Transfus; 26:207-214 1981

Immunopathologic studies of affected individuals and carrier females from 25 kindreds exhibiting the X-linked lymphoproliferative syndrome (XLP) were carried out. XLP is a combined, variable immune deficiency with four phenotypes, all apparently triggered by Epstein-Barr virus (EBV) infection: (1) fatal infectious mononucleosis (IM), (2) chronic IM progressive to malignant lymphoma, (3) acute IM progressive to acquired agammaglobulinemia, and (4) malignant lymphoma. The clinical and pathological manifestations of XLP mimic the graft-versus-host reaction. Cytogenetic studies have revealed a spectrum from no appreciable defects to extensive aneuploidy in both peripheral lymphocytes and early passage lymphocytic lymphosarcoma cells; both affected and carrier individuals show a propensity to chromosome damage. Only weakly reactive anti-EBV antibodies are found, and anti-EBV nuclear antigen is lacking in affected individuals. Specific histopathology of the four phenotypes is discussed. These findings support the hypothesis that in XLP an immune deficiency toward EBV permits chronic and fatal lymphoproliferative responses to EBV infection. If this hypothesis is accurate, genetic counseling, providing of high titer gamma globulin, and antiviral therapy may be of prophylactic use. (58 Refs)

14. IMMUNOLOGICAL ALTERATIONS IN PATIENTS WITH HODGKIN'S DISEASE IN CLINICAL REMISSION AND RELAPSE.

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Medicina (B Aires); 41(3):287-292 1981

Of 35 Hodgkin's disease patients, 21 were in remission (12-77 yr old, av 44.2 yr; 15 men and 6 women) and 14 had clinical symptoms. The relapse patients (19-76 yr old, av 40.3 yr) were: six with firm nodules, six with mixed cellularity, and one with lymphocyte depletion. Remission patients were: 16 with mixed cellularity, 3 firm nodules, and 2 with lymphocyte prevalence. Following tests were performed: proteinogram, microimmunoelectrophoresis (MIE), EAC and E rosettes, anti-Epstein Barr virus (EBV) antibody titers (anti-viral capsid antigen and anti-Epstein Barr nuclear antigen), phytohemagglutinin (PHA) stimulation, purified protein derivative (PPD) skin test, and mixed lymphocyte culture (MLC) against HRIK lymphoblastoid cell line. All patients showed significant decrease in the absolute number of T lymphocytes and EAC rosettes, but high anti-EBV antibodies (especially during clinical relapse). Pa-

tients in relapse had low PHA response, low MLC value, and negative skin test. Alterations in MIE were evident in 13 patients. Hodgkin's disease relapse patients showed severe immunity alterations. (17 Refs) (In SPA)

15. INTEGRATION OF HEPATITIS B VIRUS DNA INTO THE GENOME OF LIVER CELLS IN CHRONIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA. STUDIES IN PERCUTANEOUS LIVER BIOPSIES AND POST-MORTEM TISSUE SPECIMENS.

Shafritz DA, Shouval D, Sherman HI, Hadziyannis SJ, Kew MC
Dept. Medicine, Liver Res. Center, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, NY, 10461
N Engl J Med; 305(18):1067-1073 1981

Recombinant-DNA technology combined with gel electrophoresis was used to find hepatitis B virus DNA (HBV-DNA) in liver and tumor tissue from patients with hepatocellular carcinoma and chronic liver disease, and to study integration of HBV-DNA into the genome of the tissue cells. HBV-DNA analysis was performed on hepatocellular carcinomas from 20 patients, all of whom had at least one serological marker indicating intercurrent or previous HBV infection. Twelve patients whose sera were positive for hepatitis B surface antigen (HBsAg) had integrated HBV-DNA in the tumor; 3/8 who were HBsAg negative but positive for antibody to HBsAg (anti-HBs) also had HBV-DNA integration. Five patients who were HBsAg negative but anti-HBs positive had no detectable HBV-DNA in their tumors. In some patients integrated HBV-DNA was also found in nontumorous liver tissue with the same or different hybridization pattern from that of tumor. In five HBsAg carriers with evidence of the carrier state and chronic liver disease for less than 2 yr, HBV-DNA was present but not integrated in liver tissue. In two patients who carried HBsAg for greater than 8 yr, HBV-DNA was integrated into the host genome. The studies suggest that integration of HBV-DNA into hepatocytes occurs during the course of persistent hepatitis B virus infection and precedes development of gross neoplasm. (22 Refs)

16. DYNAMICS OF EPSTEIN-BARR VIRUS ANTIBODIES IN HODGKIN'S DISEASE.

Vanecek K, Holy J, Hrodek O, Hynieova H, Ptrtylova K, Srajer J
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Cesk Pediatr; 36(8):449-452 1981

The dynamics of antibodies to Epstein-Barr Virus capsid antigen (VCA/EBV) was studied in 38 children (26 boys and 12 girls) with Hodgkin's disease (HD). The course of the disease was protracted with remissions and recurrences in 16 cases (Group A), short, with death in a short time in 5 (Group B), and 17 other patients (Group C) were in remission without recurrence for 3-5 yr after treatment. The treatment consisted of radiotherapy followed by single-agent or polychemotherapy with cyclophosphamide, vinblastine, prednisone, and procarbazine. The antibody titer correlated with the severity and course of the disease, dropping rapidly from a very low level in Group B, and rising from higher initial levels in Group A and especially C. The antibody titers were not affected by the treatment. (7 Refs) (In CZE)

17. EPSTEIN-BARR VIRUS: ITS SITE OF PERSISTENCE AND ITS ROLE IN THE DEVELOPMENT OF CARCINOMAS.

Wolf H, Wilmes E, Bayliss GJ
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Haematol Blood Transfus; 26:191-196 1981

A review of the role of Epstein-Barr virus (EBV) in carcinoma is presented. The site of EBV persistence in the body, the antibodies to EBV-specified antigens in carcinomas of the postnasal space and other locations within the Waldeyer's ring, and the cell-fusion ability of EBV-infected cells are detailed, and the possible significance of these findings is discussed. (27 Refs)

18. SOME RECENT TRENDS IN STUDIES OF HUMAN LYMPHOID CELLS: B-CELLS, EPSTEIN-BARR VIRUS, AND TRANSFORMATION.

Zeuthen J, Klein G
Institute for Human Genetics, Bartholin Byggningen, Aarhus Univ., 8000 Aarhus C, Denmark
Haematol Blood Transfus; 26:179-190 1981

A review of recent findings in work on regulatory mechanisms involved in the selective expression of differentiated markers in human B-cell lines and the types of controls involved in the expression and function of Epstein-Barr virus (EBV)-associated markers in human cells, with special attention to the relationship between the expression of EBV functions and the expression of transformation. Because EBV is a lymphotropic virus in man, infection of lymphoid cell lines is reviewed. Chromosome studies on lymphoblastoid cell lines and B-cell lines of BL origin with regard to ploidy and karyotype abnormalities following EBV infection are discussed in detail. Studies of the immunoglobulins synthesized and the major histocompatibility antigens expressed by hybrid lymphocytes are presented. The expression of EBV, the EBV-determined nuclear antigen, and cell transformation by EBV are thoroughly reviewed. (79 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

19. SPONTANEOUS AND INDUCED HERPESVIRUS GENOME EXPRESSION IN MAREK'S DISEASE TUMOR CELL LINES.

Calnek BW, Shek WR, Schat KA
Dept. Avian and Aquatic Animal Medicine, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Infect Immun; 34(2):483-491 1981

We incubated 31 newly established Marek's disease tumor cell lines at 41 C for 48 hr after subculturing and then examined them to determine the spontaneous rates of expression of viral internal antigen(s), viral membrane antigen(s), and virus isolation. All but two of the lines were isolated from tumors induced by clone-purified Marek's disease virus strains JM-10, GA-5, RB-1B, and BC-1A in nine different genetic strains of chickens with defined histocompatibility antigens. The line-to-line variations in the rates of spontaneous expression for the antigens or virus rescue were great, but the levels of expres sion were very low in most cases. The median rates of expression for viral internal antigen, viral membrane antigen, and

virus isolation were 32, 8, and 2 positive cells per 10(5) cells, respectively (ranges, 0 to 20,280, 0 to 22,990, and 0 to 220 positive cells per 10(5) cells, respectively). The ratio of viral internal antigen expression to virus isolation was extremely variable and often high, whereas the ratio of viral internal antigen to viral membrane antigen expression was more consistent and generally low. The virus strain which induced the cell line influenced the level of virus genome expression, but the cell genotype did not. Cell lines transformed by JM-10 virus, which exhibited low oncogenicity, had significantly (p less than 0.01) higher rates of expression than cell lines transformed by GA-5 and RB-1B viruses, which exhibited high oncogenicity. Treatment with iododeoxyuridine or incubation at 37 C induced increased rates of expression in most lines but not in all lines. The degree of enhanced expression was inversely proportional to the rate of spontaneous expression. (Author abstract) (32 Refs)

20. NONLYTIC SIMIAN VIRUS 40-SPECIFIC 100K PHOSPHOPROTEIN IS ASSOCIATED WITH ANCHORAGE-INDEPENDENT GROWTH IN SIMIAN VIRUS 40-TRANSFORMED AND REVERTANT MOUSE CELL LINES.

Chen S, Verderame M, Lo A, Pollack R
Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
Mol Cell Biol; 1(11):994-1006 1981

The two distinct growth controls of normal fibroblasts can be assayed as requirements for serum or anchorage. Interaction of mouse 3T3 fibroblasts with simian virus 40 (SV40) generates four lines of transformed (TR) cells (fully TR, anchorage TR, serum TR and fully reverted). Viral gene expression was studied in these four lines. Immunoprecipitation of (35S)methionine labeled cell extracts with an antiserum from tumor-bearing hamsters detected the SV40 large T and small t proteins (94,000 mol wt [94K], 17K) and the nonviral host 54K protein in all four lines. A 100K tumor antigen was found in some, but not all lines; similar molecules have been reported in many rodent transformed lines. Analysis of the relation of phenotype to relative amounts of the various proteins in the cell classes, using the Spearman rank correlation test, showed the amount of 100K T antigen relative to 94K T antigen or to total viral protein correlated well with ability to form colonies in semisolid medium. No significant correlation was found between quantities of labeled 94K T antigen, 54K host antigen, or 17K t antigen and either serum or anchorage independence. Mouse cell TR with small t SV40 deletion mutant 884 synthesized a 100K T antigen, suggesting small t is not required. The 100K T antigen migrated more slowly than the lytic T. It is concluded that since mixtures of extracts from cells expressing and lacking the 100K T antigen yielded the expected amount of this protein, it is unlikely that the 100K T derives from the 94K protein by a posttranslational modification. (70 Refs)

21. CYTOMEGALOVIRUS CAUSES A LATENT INFECTION IN UNDIFFERENTIATED CELLS AND IS ACTIVATED BY INDUCTION OF CELL DIFFERENTIATION.

Dutko FJ, Oldstone MB
Dept. Immunopathology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
J Exp Med; 154(5):1636-1651 1981

Murine cytomegalovirus (MCMV) productively infected differentiated murine teratocarcinoma (MTC) cell lines, but did not productively infect undifferentiated MTC cell lines. Undifferentiated and differentiated cells bound similar amounts of radioactively labeled virus. In undifferentiated cells replication of infectious virus, viral antigens, or viral RNA did not occur until the cells were induced to differentiate. (51 Refs)

22. COMPARISON OF T ANTIGEN-ASSOCIATED HOST PHOSPHOPROTEINS FROM SV40-INFECTED AND -TRANSFORMED CELLS OF DIFFERENT SPECIES.

Fanning E, Burger C, Gurney EG
Fakultat fur Biologie, Universitat Konstanz, D-7750 Konstanz, W. Germany
J Gen Virol; 55(part2):367-378 1981

Simian virus 40 (SV40)-infected and -transformed cells contain, in addition to the virus-coded tumor antigens, one or more 48K to 56K host tumor antigens. At least part of this class of host proteins exists as a fast-sedimenting complex with the SV40 large T antigen. The host proteins associated with the large T antigen in SV40-transformed monkey, mouse and human cells and SV40-infected monkey cells were compared by two-dimensional gel electrophoresis and V8 partial proteolysis peptide mapping. Although these proteins differed slightly in apparent mol wt and peptide pattern, they migrated identically in isoelectric focusing gels. These results suggest tnat the cellular proteins associated with large T antigen in different hosts are very closely related to each other. Despite their similarities, the 55K proteins from different host cells form complexes of different stabilities with large T antigen, as judged by spontaneous dissociation of the complexes during storage, and the fractions of the 55K cellular protein and large T antigen found free and in the complexed form in each different host cell. (Author abstract) (36 Refs)

23. HERPES SIMPLEX VIRUS TYPE 1 AND 2 INTRACELLULAR P40: TYPE-SPECIFIC AND CROSS-REACTIVE ANTIGENIC DETERMINANTS ON PEPTIDES GENERATED BY PARTIAL PROTEOLYSIS.

Heilman CJ, Zweig M, Hampar B
Lab. Molecular Virology, Carcinogenesis Intramural Program, NCI, Frederick, MD, 21701
J Virol; 40(2):508-515 1981

Intracellular p40 is a class of protein ranging in mol wt from 39,000 to 45,000 that is immunoprecipitated from herpes simplex virus type 1 (HSV-1)- and HSV-2-infected cell extracts by mo use monoclonal antibodies or guinea pig antisera against HSV-1 and HSV-2 nucleocapsid p40. Analysis by a two-dimensional gel system showed that HSV-1 and HSV-2 intracellular p40 each consisted of three major components. However, these HSV-1 and HSV-2 proteins differed in charge and size. Analysis of Staphylococcus aureus V8 protease partial digests by two-dimensional gel electrophoresis indicated that none of the peptides of HSV-1 and HSV-2 intracellular p40 were identical. Immunoprecipitation of the partial digest products of intracellular p40-1 and p40-2 with homologous and heterologous guinea pig antisera resulted in the precipitation of various combinations of peptides indicating the presence of either type-specific or cross-reactive antigenic determinants. (Author abstract) (17 Refs)

24. CELL SURFACE T ANTIGEN IN CELLS INFECTED WITH SIMIAN VIRUS 40 OR AN ADENOVIRUS-SIMIAN VIRUS 40 HYBRID, AD2+D2.

Ismail A, Baumann EA, Hand R
McGill Cancer Centre, Dept. Medicine, McGill Univ., Montreal, Quebec H3G 1Y6, Canada
J Virol; 40(2):615-619 1981

Cell surface T antigen, detected by a radioimmune assay that uses 125I-labeled Staphylococcus aureus protein A and antibodies against either authentic T antigen or D2 hybrid T antigen, was found in simian virus 40-transformed and -infected cells and in cells infected with an adenovirus-simian virus 40 hybrid, Ad2+D2. In simian virus 40 lytic infection, the surface T antigen appeared at the same time as the nuclear T antigen. (Author abstract) (22 Refs)

25. TRANSCRIPTION OF THE SIMIAN VIRUS 40 GENOME IN DNA-TRANSFORMED MURINE TERATOCARCINOMA STEM CELLS.

Linnenbach A, Huebner K, Croce CM
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Proc Natl Acad Sci USA; 78(10):6386-6390 1981

To study the molecular basis for lack of expression of the simian virus 40 (SV40) early region genes in murine teratocarcinoma-derived stem cells, we introduced a recombinant plasmid consisting of pBR322 linked to the herpes simplex virus Type 1 thymidine kinase gene and SV40 genome into thymidine kinase-deficient F9 stem cells. The resulting stem cell clone, 12-1, and a retinoic acid-induced differentiated daughter cell clone, 12-1a, each contain one copy per cell of the entire recombinant plasmid integrated into the cellular genome through a site on the pBR322 genome. Restriction endonuclease analyses indicate that there is no difference in integration site or organization of the three component parts of the plasmid genome within cellular DNA of stem and differentiated cells; yet the differentiated cells, 12-1a, express SV40 large tumor antigen whereas the stem cells, 12-1, do not. Both stem and differentiated cells produce two size classes of polyadenylated RNA, 2,900 and 2,600 bases in length, homologous to the early region of the SV40 genome, detectable by RNA blotting analysis. S1 nuclease analysis of the SV40 transcripts present in stem and differentiated cells indicate that the SV40 mRNAs were identically spliced in the two cell types, in a manner consistent with that observed for spliced large and small tumor antigen mRNAs in SV40-infected monkey kidney cells. Thus, the failure of 12-1 teratocarcinoma stem cells, containing an integrated SV40 genome, to express SV40 tumor antigen is not due to a lack of transcription of the SV40 early region or to an inability to splice primary transcripts. (Author abstract) (44 Refs)

26. REPLICATION OF VIRAL DNA SEQUENCES INTEGRATED WITHIN THE CHROMATIN OF SV40-TRANSFORMED CHINESE HAMSTER LUNG CELLS.

Marchionni MA, Roufa DJ
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Cell; 26(2,part2):245-258 1981

To determine when during S phase integrated viral DNA sequences in several tsA SV40-transformed Chinese hamster cell clones replicate, we pulse-labeled cultures with BrdUrd and subsequently collected mitotic cells during sequential time intervals. Restriction endonuclease mapping indicated that each of the three SV40-transformed Chinese hamster lung cell clones contained a single viral DNA sequence at a different, but in each case unique, chromosomal site. DNA was extracted from each population of mitotic cells and then was resolved into dense, BrdUrd-containing and light, unsubstituted DNA fractions by cesium chloride gradient centrifugation. In each pair of samples obtained, we measured viral DNA sequences by soln hybridization using single-stranded SV40 32P-labeled DNA probes. Our results support the conclusions that specific genes within a mammalian DNA are programmed to replicate at particular times during S phase, and that the SV40 A gene product, large T antigen, programs integrated viral DNA sequences to replicate very early in S phase. The fractions of viral DNA replicated early in S phase appeared to correlate with each clone's content of functional large T antigen at permissive and nonpermissive culture temperatures. (Author abstract) (96 Refs)

27. MARKER PROFILES OF LEUKEMIA-LYMPHOMA CELL LINES.

Minowada J
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Haematol Blood Transfus; 26:323-325 1981

Marker profiles (eg, Ia antigen, myelomonocyte antigen, immunoglobulins, Epstein-Barr virus) of 50 leukemia-lymphoma cell lines are presented. The cell lines are divided into three groups: T cell, B cell, or non-T, non-B cells. (4 Refs)

28. PERSISTENCE OF NON-INTEGRATED VIRAL DNA IN BOVINE CELLS TRANSFORMED IN VITRO BY BOVINE PAPILLOMAVIRUS TYPE 2.

Moar MH, Campo MS, Laird H, Jarrett FH
Dept. Zoology, Univ. Edinburgh, West Mains Road, Edinburgh EH9 3JT, Scotland
Nature; 293(5835):749-751 1981

The presence and maintenance of bovine papillomavirus 2 (BPV 2) in bovine cells transformed in vitro by BPV 2 was studied. Two of the cell lines (12CON/BPV 2 and 16CON/BPV 2) arose from infection of bovine conjunctiva at the 12th and 16th passage, and another (17PAL/BPV 2) arose from infection of the bovine palate at the 17th passage. High-mol wt DNA was prepared from each cell line at various passages and cleaved with the restriction enzyme EcoRI, HindIII, and HindII. Cleaving with these enzymes produced DNA fragments which co-migrated with fragments produced by cleaving BPV 2 DNA. Each cell line contained multiple copies of the BPV 2 genome, ranging from 33-55 viral genome equivalents per diploid quantity of cell DNA. Cells in each line contained disproportionate amounts of viral DNA. No evidence of virus or viral antigens was found in the three cell lines. These findings constitute the first detection of papillomavirus DNA in in vitro transformed cells of the natural host. These findings could be significant in terms of the analysis of oncogenic virus-cell interactions. The results underline further the difficulty in establishing suitable in vitro tissue culture systems to propagate papillomavirus. (27 Refs)

29. EPSTEIN-BARR VIRUS-INDUCED PROTEINS. IV. CHARACTERIZATION OF AN EBV-ASSOCIATED PHOSPHOPOLYPEPTIDE.

Mueller-Lantzsch N, Yamamoto N
Schweizerisches Serum und Impfinstitut, Bern, Switzerland
J Gen Virol; 55(part2):333-341 1981

Cells of the Epstein-Barr virus (EBV) non-producing lines NC37 and Raji were induced by the tumor promoter TPA and were labelled with 32P. The analysis by immunoprecipitation with human VCA+EA+ sera revealed that a major phosphopolypeptide with a mol wt of 58,000 was specifically precipitated. In addition, a phosphopolypeptide of the same size was the dominant phosphopolypeptide detected in EBV-producing B95-8 and P3HR-1 cells as well as in P3HR-1-superinfected NC37 cells. This phosphopolypeptide seemed to be EBV-specific, because it was not detectable in TPA-treated, but EBV genome-negative, Ramos and BJAB cells. Synthesis of this phosphopolypeptide was inhibited in TPA-treated NC37 cells by treatment with Ara-C. VCA+EA+ sera were found to be more immunoreactive with this phosphopolypeptide than VCA+EA- or EBNA+ sera. Based on these results this phosphopolypeptide may have some immunological relatedness to the EBV-specific early antigen (EA) complex defined by immunofluorescence. (Author abstract) (29 Refs)

30. ONCOGENIC ACTIVITY OF THE BK TYPE OF HUMAN PAPOVA VIRUS IN NEWBORN WISTAR RATS.

Noss G, Stauch G, Mehraein P, Georgii A
Institut fur Virologie und Seuchenhygiene, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany
Arch Virol; 69(3/4):239-251 1981

The oncogenic potential of the human papova virus BK (= BKV) has been examined i n newborn Wistar rats. Twelve of 37 animals inoculated with BKV sc and 7 of 40 animals inoculated with BKV ic developed tumors of various histological types. The latency periods ranged from 6 to 18 mo. The BKV etiology of tumors was supported by detection of BKV T antigen in cells of established tumor lines by means of indirect immunofluorescence. No tumors appeared in animals given injections of saline instead of virus. BKV T antibodies were detected in sera of 100% of animals bearing tumors but not in sera of control animals. Only 3 of 77 BKV infected and none of the control animals developed spontaneous tumors (adenomas). (Author abstract) (16 Refs)

31. KINETICS OF INHIBITION OF PAPOVAVIRUS DNA SYNTHESIS BY SUPERINFECTION WITH ADENOVIRUS 2 AND NON-DEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Patch CT, Howley PM, Hauser J, Levine AS
Section Infectious Disease, Pediatric Oncology Branch, NCI, NIH, Bethesda, MD, 20205
J Gen Virol; 55(part2):355-365 1981

Simian Virus 40 (SV40) DNA synthesis is inhibited in monkey cells by superinfection with adenovirus 2 (Ad2) and various non-defective Ad2-SV40 hybrid viruses. Similarly, BKV (a human papovavirus) DNA synthesis is inhibited in human cells by superinfection with Ad2. Kinetic studies indicate that inhibition begins during the early phase of the Ad2 lytic cycle. Superinfection with Ad2 does not significantly alter the formation of SV40 T antigen. Superinfection with Ad2 late in the SV40 lytic cycle is less efficient in the inhibition of SV40 DNA synthesis, and the onset of Ad2 DNA synthesis is delayed, compared to superinfection early in the SV40 lytic cycle. These findings suggest that the Ad2 and SV40 genomes may compete to bind an early Ad2 protein which is essential for Ad2 replication, but which blocks SV40 replication. (Author abstract) (28 Refs)

32. CORRELATION OF IN VITRO PROPERTIES AND TUMOURIGENICITY OF HAMSTER KIDNEY CELLS TRANSFORMED BY BK VIRUS.

Possati L, De Luca S, Ciarallo G, Portolani M
Inst. Microbiology, Univ. Ancona, Via Grotte di Posatora, 60100 Ancona, Italy
J Gen Virol; 55(part2):481-486 1981

Hamster kidney cells transformed by BK virus (HKBK cells) were studied at low passage (about 30 subcultures) after transformation and at high passage (about 130 subcultures) after transforming. Several in vitro properties (rescue of virus, presence of T antigen, colony formation on plastic, in soft agar, on monolayers of normal cells, and serum dependency of growth) and tumorigenicity of these cells for newborn and adult hamsters were compared. HKBK cells at low passage showed high levels of T antigen, the growth properties of normal cells and low tumor-producing ability, while HKBK cells at high passage showed low levels of T antigen, the growth properties of transformed cells and high tumor-producing abi lity. These results may indicate that cellular transformation by BK virus is initiated, but not maintained, by the expression of genes regulating T antigen, and that the maintenance of the transformed state is due to complicated cellular and viral gene interactions occurring during the course of cell life. (Author abstract) (18 Refs)

33. BINDING OF DEPHOSPHORYLATED A PROTEIN TO SV40 DNA.

Shaw SB, Tegtmeyer P
(c/o Tegtmeyer) Dept. Microbiology, State Univ. New York, Stony Brook, NY, 11794
Virology; 115(1):88-96 1981

We have examined the role of SV40 A protein (T antigen) phosphorylation in the specific binding of the protein to SV40 DNA using protein that was dephosphorylated in vitro. Alkaline phosphatase removed more than 75% of the phosphate radiolabel associated with the A protein. Most of the phosphoserine residues were sensitive to the enzyme while most of the phosphothreonine residues were resistant. Phosphopeptide mapping of the dephosphorylated protein demonstrated that the phosphate groups at individual sites were either highly sensitive or highly resistant to the phosphatase. Thus, enzymatically dephosphorylated A protein provides a useful probe for analysis of the function of specific phosphorylation sites. Dephosphorylated A protein, like untreated A protein, preferentially bound a restriction fragment of SV40 DNA that contains the origin of DNA replication and sequences involved in transcriptional control. The binding was characterized further using a DNase protection assay and DNase footprinting. Dephosphorylated A protein protected SV40 DNA in a manner that was indistinguishable from that of untreated protein. The effects of A protein concentration and salt treatment on binding were the same for phosphatase-treated and control untreated A protein under the conditions of our assay. These results suggest that the location, alignment, and affinity of binding are unaffected by dephosphorylation. We conclude that phosphorylation at the majority of the phosphoserine sites is not directly involved in the regulation of site-specific recognition and bind-

ing of the A protein to SV40 DNA. (Author abstract) (23 Refs)

34. ONCOGENICITY OF HEAT-INACTIVATED SIMIAN ADENOVIRUS SA7.

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Paul-Ehrlich-Institut, Paul-Ehrlich-Strasse 42-44, D-6000 Frankfurt a. M., W. Germany
Arch Virol; 69(3/4):189-196 1981

Simian adenovirus SA7 heated for 30 min at 70 C retained part of its ability to induce tumors in newborn hamsters. Tumors were also induced by DNA extracted from the heated virus. However, neither residual replicating, ie cytopathogenic, nor transforming and T-antigen-inducing activities could be detected in vitro in CV-1 and hamster embryo cells inoculated with the heated virus. The results are discussed in terms of a possible release of viral nucleic acid at the high temperature. They also show t hat current tests for effective virus inactivation based exclusively on the recognition of replicating virus should be reevaluated. (Author abstract) (19 Refs)

35. ESTABLISHMENT AND CHARACTERIZATION OF PERMANENT CELL LINES FROM PATIENTS WITH ACUTE AND HAIRY CELL LEUKEMIA.

Stockbauer P, Cinatl J, Mach O
Inst. Hematology and Blood Transfusion, 128 20 Prague, Czechoslovakia
Neoplasma; 28(4):385-395 1981

Four cell lines were established from peripheral blood of patients with leukemia. All lines express the Epstein Barr virus nuclear antigen (EBNA) and therefore should be classified as lymphoblastoid cell lines. However, one of the lines UHKT-5 established from a patient with acute myelomonocytic leukemia has some features not typical for lymphoblastoid cell lines. The cells resemble macrophages with the phagocytic ability for yeasts, strong alpha-naphthylacetate esterase positivity in phagocytizing cells and unusually long villi. Another line UHKT-7 established from a patient with hairy cell leukemia expresses the same isotype of membrane Ig as the original hairy cells. (Author abstract) (26 Refs)

36. ANALYSIS OF THE TRANSFORMATION OF HUMAN LYMPHOCYTES BY EPSTEIN-BARR VIRUS III. INDUCTION OF EARLY EVENTS BY P3HR-1 STRAIN WITHOUT SUBSEQUENT IMMORTALIZATION.

Takada K, Osato T
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Med Microbiol Immunol (Berl); 170(1):19-26 1981

The interaction between Epstein Barr virus (EBV) derived from P3HR-1 cell line and human cord blood lymphocytes was studied by simultaneous observations of events occurring in EBV-induced transformation in individual cells. EBV derived from B95-8 cells (B95-8 EBV) was used for positive control. B95-8 EBV induced a complete series of early transformation events including nuclear antigen (EBNA) and DNA synthesis and blastogenesis, followed by immortalization of the infected lymphocytes. When the same cord preparation was exposed to P3HR-1 EBV, EBNA-positive cells were clearly identified even 12 hr after viral exposure and reached a max of 31% at 24 hr, followed by a plateau for a subsequent 24 hr. In contrast to B95-8 EBV infection, EBNA staining was weak. At 24 hr, blastogenesis was also significant while 3H-thymidine incorporation was not. In addition to weak fluorescence, brilliant EBNA staining later occurred at 48 hr and reached about 20% of the total positive cells on day 5. The EBNA-positive blast cells then became grain-positive at 36 hr and the immunofluorescent cells reached 61.1% at 120 hr. At this time, nearly 50% of the stained nuclei showed evidence of DNA synthesis. At 72 hr, all examined mitotic cells were positive for EBNA and the mitotic frequency was as high as that seen in B95-8 EBV infections. Characteristic cell aggregates were also seen. The number of infected cells decreased gradually afte r 1 wk and degenerated in about 2 wk. Essentially the same results were obtained, using different stocks of EBV derived from both P3HR-1 sublines A and B and different cord cell preparations. The results indicated that P3HR-1 virus does retain early transforming functions for primary human B lymphocytes, although infected cells have a short life span. (28 Refs)

37. PHENOTYPIC CHANGE OF AN SV40-TRANSFORMED MOUSE MACROPHAGE LINE, BB-W-531-2, INDUCED BY DIFFERENT CULTURAL METHODS.

Takayama H, Tanigawa T, Takagi A
Dept. Bacteriology, Tottori Univ. Sch. Medicine, Yonago, Tottori 683, Japan
Microbiol Immunol; 25(8):827-835 1981

The effect of culture methods on the characteristics of Simian virus 40 (SV40)-transformed macrophages, BB-W-531-2, established from BALB/cAN mouse bone marrow cells was studied. Results indicated that cell growth and differentiated cell properties of clonal macrophages (BB-W-531-2 line) are controlled by culture methods. The cells passaged by the first method showed a reversible transition between the macrophage and non-macrophage states depending upon cell density. The cell passaged by the second method retained their macrophage properties throughout the culture and grew very slowly. The cells passaged by the third method did not show density-dependent transition. Macrophage properties, such as immune phagocytosis, seemed to be induced by diffusible factor(s) produced by cells possessing such properties. The fact that several properties of BB-W-531-2 cells can be controlled by the culture methods described above suggested the potential value of such control in studies of gene expression regulation. BB-W-531-2 cell growth was correlated with the intensity of SV40 T-antigen and seemed to be suppressed in poor-spreading conditions such as confluent cell density or cultivation on bacteriologic dishes. The development of macrophage properties in cultures of confluent density suggested that both density-dependent grow inhibition and diffusible factors are probably required for induction of macrophage properties. (20 Refs)

38. ANTISERUM TO SV40 T ANTIGENS FROM A RABBIT INOCULATED WITH AUTOCHTHONOUS CELLS TRANSFORMED IN VITRO BY SV40.

Tamura H, Shimura H, Kimura G
First Dept. Surgery, Tottori Univ. Sch. Medicine, Nishimachi 36-1, Yonago 683, Japan
Gan; 72(5):769-771 1981

A morphologically transformed cell line was established after infection with SV40 of the primary culture derived from a kidney removed surgically from a rabbit. The transformed cells were free of detectable infectious SV40 particles but produced them upon fusion with permissive monkey cells, and produced SV40-specific large and small T antigens. Repeated sc inoculations of the transformed cells into the animal from which the parental kidney cells had been derived failed to result in tumor formation but raised a substantial level of anti-

bodies to the SV40-specific large and small T antigens as well as to the 58,000 dalton mol wt cellular protein (middle T antigen) (Author abstract) (10 Refs)

39. PARTIAL PURIFICATION OF SV40 A PROTEIN AND A RELATED CELLULAR PROTEIN FROM PERMISSIVE CELLS.

Tegtmeyer P, Andersen B
Dept. Microbiology, State Univ. New York, Stony Brook, NY, 11794
Virology; 115(1):67-74 1981

A simple and reproducible method for the purification of SV40 A protein (T antigen) from permissive cells has been developed. Two cellular proteins are also purified in smaller quantities by the same procedure. The cellular proteins have mol wt similar to undegraded SV40 A protein. Peptide maps of the viral and cellular proteins are not similar but one of the cellular proteins apparently shares limited antigenicity with the SV40 A protein. (Author abstract) (10 Refs)

40. ALTERNATIVE INTERACTIONS OF THE SV40 A PROTEIN WITH DNA.

Tegtmeyer P, Andersen B, Shaw SB, Wilson VG
Dept. Microbiology, State Univ. New York, Stony Brook, NY, 11794
Virology; 115(1):75-87 1981

We have characterized the DNA binding properties of SV40 A protein (T antigen) from permissive cells. The viral protein protects 110-to 115-, 60-to 65-, 40-to 45-, and 30-to 35-bp fragments of SV40 DNA from an excess of DNase I. The 60-to 65-bp fragment extends some 30-35 bp to either side of the BglI site at the origin of replication. DNase footprinting confirms the location of this binding region and shows that it is the most completely protected DNA binding site under our conditions. The A protein selectively recognizes the 60-to 65-bp origin fragment in the complete absence of adjacent DNA and binds to it in three alternative ways that protect 60-65, 40-45, or 30-35 bp from nuclease. Thus these three interactions with isolated origins recapitulate the binding of viral protein to intact SV40 DNA. We propose that the alternative interactions of SV40 A protein with the 60-to 65-bp origin fragment may represent three different conformational alignments of protein with DNA rather than a simple repetition of a single kind of binding interaction. Viral protein also protect pBR322 and lambda phage DNA from nuclease to a limited extent. Similar interactions could possibly alter the function of DNA control regions of host cells. (Author abstract) (15 Refs)

41. MONOCLONAL ANTIBODY AGAINST A BURKITT LYMPHOMA-ASSOCIATED ANTIGEN.

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Laboratoire d'Immunologie Clinique, Institut Gustave-Roussy, 94800 Villejuif, France
Proc Natl Acad Sci USA; 78(10):6485-6488 1981

A monoclonal antibody, referred to as 38.13, was obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma containing Epste in-Barr virus genome but lacking HLA-A, -B, and -C and beta2-microglobulin molecules at the cell surface). 38.13 antibody was demonstrated to be a rat IgM. By complement-dependent microcytotoxicity and indirect immunofluorescence assays, 38.13 antibody was shown to react specifically with cells derived from Burkitt tumors, including both Epstein-Barr virus genome-carrying and Epstein-Barr virus-negative Burkitt lymphoma. By contrast, Epstein-Barr virus-containing lymphoblastoid cell lines derived from normal B lymphocytes were not recognized by 38.13 antibody. Fresh malignant cells from patients affected with various lymphoproliferative disorders were negative, except 4/8 having abdominal Burkitt-like lymphomas. Normal lymphocytes from peripheral blood, spleen, lymph node, tonsil, and bone marrow and mitogen (phytohemagglutinin, pokeweed mitogen, and concanavalin A)-activated blasts were also negative. Thus, 38.13 antibody apparently recognized a Burkitt-associated antigen that is not related to Epstein-Barr virus. The pattern of reactivity of 38.13 antibody with various Burkitt lymphoma cells appeared quite heterogenous and some Burkitt cells were consistently negative. 38.13 antibody thus defines a subset of Burkitt lymphomas. (Author abstract) (18 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

42. GENETIC APPROACHES TOWARD ELUCIDATING THE MECHANISMS OF TYPE-C VIRUS-INDUCED LEUKEMIA.

Aaronson SA, Barbacid M, Dunn CY, Reddy EP
Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014
Haematol Blood Transfus; 26:455-459 1981

The mechanisms of induction of leukemia by murine type-C viruses was studied in newborn NIH/Swiss mice. Inoculations of 5 x 10(4) XC pock forming units of either Rauscher (R) or Moloney (M) murine leukemia virus (MuLV) produced gross enlargement of spleen and lymph nodes as early as 10-11 wk. RMuLV produced spleen enlargement and sometimes liver and peripheral or visceral lymph node enlargement. MMuLV produced thymus enlargement in most animals, and frequently affected other lymphoid organs. MMuLV-induced tumors were of T cell origin, as indicated by presence of Thy1 antigen and absence of Fc or C3 receptors. RMuLV-induced tumors were of B cell lineage, as indicated by presence of Fc receptors and absence of Thy1 antigen. Recombinant forms between oncogenic and nononcogenic type-C viruses were produced in wild mouse embryo cells of line WM-C. These recombinants contained genetic information in varying amounts from both parental viruses and exhibited varying degrees of oncogenicity. Results indicate that target cells for transformation by RMuLV and MMuLV contain specific markers distinguishing them from other lymphoid elements. The necessity of active virus replication for tumorigenesis by murine type-C viruses is suggested. (19 Refs)

43. ELECTRON-MICROSCOPIC IMMUNOCYTOCHEMICAL AND FUNCTIONAL INVESTIGATIONS OF NORMAL AND LEUKEMIA VIRUS INFECTED BONE MARROW MONONUCLEAR CELLS (MEETING ABSTRACT).

Butenko ZA, Zak KP, Komissarenko SV
Department of the Molecular Mechanisms Cancero- and, Leukemogenesis R.E. Kavetsky Institute Oncology Problems, Academy Science of, Ukraine Kiev, USSR
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. 92 pp., 1981.

Ultrastructure of different types of bone marrow mononuclear cells in normal and Rauscher leukemia virus infected BALB/c mice was studied. Using modern techniques of electron-microscopic immunocytochemistry including PAP method

mononuclear cells bearing membrane immunoglobulins and other antigens were detected (Thy 1.1., Thy 1.2., brain associated antigens). Bone marrow lymphocytes and lymphocyte-like mononuclear cells with different colony-forming ability were studied as such and fractionated in density gradients of high mol wt substances in vivo and in vitro. The functional and submicroscopic characteristics of different bone marrow immunoglobulin-bearing lymphocytes and hemopoietic stem cells of normal and Rauscher leukemia virus infected are presented in detail. (no Refs)

44. EXPRESSION OF THE MURINE MAMMARY TUMOR VIRUS IN THE MILK OF F1 HYBRIDS OF VIRUS NEGATIVE MOUSE STRAINS.

Bentvelzen P
Radiobiological Inst. TNO, Rijswijk, The Netherlands
Eur J Cancer Clin Oncol; 17(8):883-888 1981

Milk samples of multiparous females from several mouse strains and their F1 hybrids were tested for the presence of the envelope glycoprotein gp52 of the murine mammary tumor virous. F1 hybrids resulting from matings of the virus negative strain BALB/c with the virus negative strains AKR, ND2 or RFM were positive for the viral antigen. The progeny of backcrosses to either parent had considerable lower incidences of viral antigen-positive milks. It was concluded that different recessive genes in the BALB/c strain on the one hand and in the AKR, ND2 and RFM strain on the other cause inhibition of endogenous virus expression. In F1 hybrids the two sets of genes complement each other, resulting in virus release. (Author abstract) (31 Refs)

45. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD
Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Haematol Blood Transfus; 26:483-487 1981

The biology and natural history of the feline retroviruses and the diseases they cause are reviewed. The feline leukemia viruses (FeLV) cause several forms of leukemia and lymphoma that occur at different rates in different geographic areas; no specific association between naturally occurring disease and any strain(s) of any subgroup(s) has been demonstrated. FeLVs are replication competent and cause no visible pathology in infected cultured cells. FeLVs are transmitted in a contagious manner. Approx 2-5% of infected cats become persistently viremic, and one-fourth to one-third of these animals develop leukemia (the other develop infectious peritonitis, septicemia, or glomerulonephritis). Both leukemic and persistently viremic cats release large amounts of infectious FeLV in their saliva. FeLV appears to play an important role in the etiology of 'virus-negative' leukemia in cats; an understanding of the mechanism of this phenomenon may help us to explain human leukemias that occur in individuals that do not harbor replicating virus. FeLV particles contain seven distinct proteins, several of which have greater than 1 antigenic determinant and all of which induce immune responses in cats to some degree. The feline oncornavirus-associated cell membrane antigen (FOCMA) is found on lymphoma and/or leukemia cells, and the immune response to it is correlated with protection against development of leukemia and lymphoma. Two general classes of tumor- and transformation-specific antigens have been found. (39 Refs)

46. GROWTH OF HUMAN NORMAL AND LEUKEMIC T CELLS: T-CELL GROWTH FACTOR (TCGF) AND THE ISOLATION OF A NEW CLASS OF RNA TUMOR VIRUSES (HTLV).

Gallo RC, De The, Lajtha L, Van Bekkum DW, McCulloch EA, Greaves MJ, Seligmann M, Brecher G, Shobet SB, Bessis M, Sachs L

Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Blood Cells; 7(2):313-329 1981

Previous studies have indicated that T-cell growth factor (TCGF) is the physiological growth promoter in the immune response of T-lymphocytes, acting as the second signal (after antigen) in the immune response. A summary is presented of information on proliferation of normal T-cells in a previously described liquid suspension culture and proliferation of several new cell lines from patients with particular types of T-cell leukemias and lymphomas. Information on the new type-C virus designated HTLV is also summarized. Neoplastic T cells from patients with cutaneous T-cell leukemias and and lymphomas, eg Sezary syndrome and mycosis fungoides, were grown routinely with the use of purified TCGF free of phytohemagglutinin and of lymphokines other than TCGF. The neoplastic T cells responded directly to TCGF without prior in vitro activation with antigen or lectin as is necessary with normal T cells. Thus, transformed mature T cells already express TCGF receptors. HTLV were isolated from some of these new cell lines. Evidence is presented to indicate these may be the first unambiguous isolates of RNA tumor viruses from humans. These new viruses are easily distinguished from all previously isolated viruses from animals. Antibodies in sera of some patients with these diseases specifically react with proteins of these viruses. (11 Refs)

47. FELINE LEUKEMIA VIRUS NONPRODUCER LYMPHOSARCOMAS OF CATS AS A MODEL FOR THE ETIO LOGY OF HUMAN LEUKEMIAS.

Hardy WD, McClelland AJ, Zuckerman EE, Snyder HW, MacEwen EG, Francis D, Essex M

No affiliation given
Haematol Blood Transfus; 26:492-494 1981

Immunological and epidemiological studies of feline lymphosarcoma (LSA) are summarized. Immunofluorescent antibody assay, immunodiffusion, tissue culture isolation, and radioimmunoassay were used to test 507 casts with LSA for feline leukemia virus (FeLV). FeLV-positive LSA was found in 360 cats; the remaining 147 had nonproducer (NP) LSA. No FeLV proteins or infectious viruses were detected in NP LSA. However, the FeLV-induced tumor specific oncovirus-associated cell membrane antigen was detected on the surface of both NP and FeLV positive LSA cells. Of 1,612 FeLV-exposed and -unexposed cats observed for development of LSA, 0/1,074 unexposed cats (observed av 3 yr/cat) developed LSA; 149/538 exposed cats (observed av 4.4 yr/cat) were persistently infected. LSA developed in 41 cats, 30 FeLV positive and 11 NP LSA. Difference in rate of NP LSA in FeLV-exposed and -unexposed cats was significant (p less than 0.001). FeLV appears to be the etiologic agent of feline LSA regardless of FeLV status. Mechanisms by which RNA- and DNA-containing viruses induce tumors are discussed. Feline NP LSA could be a useful model for elucidating mechanisms of oncovirus transformation. (12 Refs)

48. ELISA FOR THE DETECTION OF ANTIGENS CROSS-REACTING WITH PRIMATE C-TYPE VIRAL PROTEINS (P30,GP70) IN HUMAN LEUKEMIC SERA.

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Haematol Blood Transfus; 26:530-536 1981

The enzyme linked immunosorbent assay (ELISA) was employed in the detection and quantification of the core protein p30 of murine leukemia viruses (MuLV), the baboon endogenous virus (BaEV) and simian sarcoma virus (SSV) and the envelope glycoprotein p70 of SSV. ELISA was successfully applied in detection and quantification of p30 in tissue culture cells, tumor cells, and sera. It was also used successfully when applied to the viral glycoprotein of SSV gp70. Reactivity of gp70 was not altered by glycosidases. Proteins reacting with antibodies against p30 of BaEV and SSV were specifically detected in leukemic sera, but not, or at only very low levels, in sera from non-leukemic patients and healthy controls. Cross-reacting antigens were detected with anti-SSV p30 IgG in 15/49 leukemic sera and with anti-BaEV-p30 IgG in 19/49 leukemic sera. Antigens cross-reacting with viral envelope glycoprotein of SSV were detected in both normal and leukemic sera. In a study of the sera of 23 patients with chronic myelogenous leukemia in blast crisis, 16 were positive for one or more structures cross-reacting with SSV gp70. The fact that many of these 16 patients had a shorter survival than the non-reactors suggests a possible prognostic role for these antigens. (19 Refs)

49. IMMUNOCHEMICAL REACTIVITY OF SIMIAN SARCOMA VIRUS POLYPEPTIDES ISOLATED BY PREPARATIVE SODIUM DODECYL SULFATE POLYACRYLAMIDE GEL ELECTROPHORESIS.

Johnson JC, Higuchi T, Geissler E

Dept. Biological Sciences, Old Dominion Univ., Norfolk, VA, 23508

Can J Microbiol; 27(2):238-242 1981

The polypeptides associated with a zonal centrifugation purified simian sarcoma virus propagated in lymphoblastoid NC-37 cells were isolated by preparative polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate (SDS) using a procedure designed to minimize the loss of immunochemical reactivity. The proteins p10, p15, p28, p36, p44, p75, and p86 were obtained in large yield and high degree of homogeneity. The electrophoretically purified p28 was analyzed by competition radioimmunoassay using antiserum to a pore exclusion and ion exchange purified simian sarcoma virus p28. Complete competition was observed with extracts of simian sarcoma virus infected cells. No competition was observed with uninfected or unrelated, infected cell extracts. The antigen-antibody affinity as measured by the slope of the competition curve using antiserum to p28 and 125I-labeled and electrophoretically purified p28 was the same as that for the p28 released from sonication-disrupted simian sarcoma virus. The data indicates that preparative purifications by polyacrylamide gel electrophoresis in the presence of SDS may be generally applicable for the isolation of proteins with essentially the same immunospecificities and affinity for a specific antiserum as proteins isolated by procedures that avoid the use of SDS and electrophoresis. (Author abstract) (21 Refs)

50. CELL FUSION AS A TOOL FOR THE DETECTION OF VIRAL FOOTPRINTS IN CHILDHOOD LEUKEMIA.

Jore J, Dubbes R, Coolen J, Nooter K

No affiliation given

Haematol Blood Transfus; 26:527-529 1981

Seven bone marrow samples from leukemic children were fused with fetal dog thymus A7573 cells and two samples were fused with rabbit cornea SIRC cells. Fused cultures were screened periodically for the presence of viral antigens by indirect cytoplasmic immunofluorescence assay (IFA), using antiviral antisera for the major 30,000 dalton internal polypeptide of murine type C virus (R-MuLV) and of primate type C virus (SiSV). Antigens appeared in 7/9 cultures 1-5 wk after fusion. IFA reaction was predominantly with SiSV antiserum: end point titers (reciprocal of highest antiserum dilution with which virus-specific cytoplasmic fluorescence was still observed) were in the range 40-80 vs less than 10-20 with R-MuLV antiserum and 10 in virus negative controls. Antigen presence was transient; after 2-3 mo the cultures were negative in the IFA. Fused cultures did not produce extracellular reverse transcriptase. Repetition of three fusion experiments with a hypoxanthine-guanine phosphoribosyl transferase mutant of A7573 offered the possibility of selection for hybrid cells, but selection did not result in higher IFA titers or reverse transcriptase production. Results show that the frequency of antigen positive cultures is comparable with that found in cocultivation experiments. However, cell fusion appears superior in that it speeds the appearance of antigens with cell passage number (1-5 wk after fusion vs 1-2 mo after starting cocultivation). The cell fusion procedure never led to overt virus production. (5 Refs)

51. INHIBITION OF ANTIGEN-INDUCED T-CELL PROLIFERATION BY ANTIBODIES TO ENDOGENOUS AKR-MULV.

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Dept. Microbiology, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia 6009, Australia

Cell Immunol; 64(1):102-118 1981

Lymph node cells from BALB/c mice immunized with ovalbumin or human gamma-globulin were restimulated in vitro with these antigens and assayed for antigen-induced proliferation. The proliferative response was shown to be antigen specific and T cell dependent. A rabbit antiserum to envelope and core proteins of AKR murine leukemia virus was found to inhibit antigen-induced T-cell proliferation. The IgG fraction and F(ab')2 fragments of the antiserum were also inhibitory. The inhibition occurred after the initial step of antigen-T cell interaction and viral absorption studies showed the inhibition to be specific for anti-AKR virus antibodies. A hypothesis for the mechanism of inhibition is discussed in relation to a functional role for endogenous murine leukemia virus. (Author abstract) (36 Refs)

52. INDUCTION OF ENDOGENOUS MAMMARY TUMOR VIRUS EXPRESSION DURING HORMONAL INDUCTION OF MAMMARY ADENOACANTHOMAS AND CARCINOMAS OF BALB/C FEMALE MICE.

McGrath CM, Prass WA, Maloney TM, Jones RF
Dept. Tumor Biology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
JNCI; 67(4):841-852 1981

Treatment of BALB/c female mice with pituitary isografts, under conditions that established mammary hyperplasia in an anovulatory condition, enhanced mammary tumor development with prior onset of dysplastic foci in lobular parenchyma. Tumor onset began at 8 mo (mean onset time, 18 mo); the 25-mo incidence was 100%. Adenoacanthomatous tumors appeared first. Adenocarcinomas appeared only after more than 14 mo of continuous hormone stimulation. Dysplastic and neoplastic changes occurred while blood levels of the three major mammotropic hormones were physiologic. Murine mammary tumor virus (MuMTV) p28 was detected in all tumors tested, independent of time of tumor appearance or tumor type, although keratinizing cells in adenoacanthomatous tumors did not contribute to MuMTV antigen expression. MuMTV gp52 was detected in only a small fraction of cells in a few tumors. MuMTV RNA contents were above normal in all tumors tested. Neither MuMTV structural antigens nor RNA was induced in normal glands by the same hormone treatment that ultimately resulted in dysplasia and tumor formation and elevated levels of these viral markers in neoplasms. The MuMTV RNA in all hormone-induced tumors was readily distinguishable in base sequence from standard MuMTV RNA but indistinguishable from MuMTV RNA recovered from lactating mammary glands of BALB/c females carrying only endogenous MuMTV proviruses, suggesting that endogenous MuMTV RNA sequences were induced in hormone-induced neoplasms. RNA indistinguishable from MuMTV sequences present in hormone-induced primary tumors was also detected in multiple genomic equivalents in two independently derived hormone-induced premalignant alveolar hyperplasias. MuMTV p28 was detected, but gp52 was not. The same hormone stimulus that generated 100% tumors in normal glands greatly accelerated tumor development in premalignant hyperplasias but did not amplify MuMTV RNA or antigens in either hyperplasias or the tumors derived from them. B-type virions were not detected in these tissues, in either hypophyseal implant-stimulated or virgin hosts. Cell-free virions were not detected in culture. These data suggest that the replication of MuMTV induced in hormone-induced neoplasms is defective. Details of its expression suggest that if involved in events leading to tumors, its involvement is insufficient cause for those tumors. (Author abstract) (41 Refs)

53. NATURAL ANTIBODIES TO BLV GP51 ARE REACTIVE AGAINST THE CARBOHYDRATE MOIETY OF THE GLYCOPROTEIN.

Portetelle D, Bruck C, Mammerickx M, Burny A
No affiliation given
Haematol Blood Transfus; 26:498-501 1981

The antigenic site of bovine leukemia virus (BLV) gp51 exposed at the cell membrane of virus-producing cells and recognized as target by sera exhibiting strong cytolytic activity towards these cells was examined. Sera 2146 and 2152 were prepared in the rabbit by injection of BLV-infected bovine lymphocytes. Sera 67 and 82 were from cattle in the tumor phase of enzootic bovine leukosis. Serum 3162 was obtained from an animal in persistent lymphocytosis and serum 351628 was derived from an asymptomatic BLV carrier. Rabbit serum 167 was raised by injection of purified BLV gp51. Natural sera 67 and 351628 exhibited strong cytolytic activity (approx 100% and 80%, respectively) compared with rabbit serum 167 (approx 2%) at reciprocal of serum dilution = 5. Competition radioimmunoassay between bovine serum 67 and rabbit serum 2146 and solid phase radioimmunoassay indicated that (1) natural and rabbit sera react with different gp51 antigenic regions, and (2) the antigenic site recognized by natural sera is unique. Glycosidase treatme nt of 125I-labeled antigen followed by addition of a variety of antisera revealed the importance of the gp51 carbohydrate moiety: sera 2152, 3162, and 67 lost reactivity almost completely (from approx 70-100% to 20% or less at log reciprocal of serum dilution = 2). However, glycosidase digestion lowered max precipitability of gp51 in the presence of serum 167 by only 20%. Protease treatment of the antigen suggests that the gp51 polypeptide backbone is the target for serum 167. (4 Refs)

54. RELATIONSHIP OF THE FELINE ONCORNAVIRUS ASSOCIATED CELL MEMBRANE ANTIGEN TO A FELINE SARCOMA VIRUS ENCODED POLYPROTEIN.

Snyder HW, Dutta-Choudhury M, Hardy Jr WD
No affiliation given
Haematol Blood Transfus; 26:488-491 1981

Using immunoaffinity chromatography on a column of Sepharose containing bound IgG from cat anti-feline oncornavirus-associated cell membrane antigen (FOCMA) serum, a 70,000-dalton protein was isolated from lysates of mink cells transformed by the Gardner-Arnstein strain of feline sarcoma virus (GA-FeSV). This result was unanticipated because previous evidence had suggested that FOCMA was associated with the much larger (95,000 dalton) gag-x fusion protein in these cells. The GA-FeSV gag-x protein was also isolated by virtue of its binding to anti-FeSV antibodies on a different affinity column. Preliminary biochemical characterization of the 70,000-dalton protein from both GA-FeSV-transformed mink fibroblasts and feline lymphosarcoma cells showed no differences between them. The gag-x protein was distinguishable by labelling with 32P-orthophosphate, association with protein kinase activity, and its precipitation ability with antibodies in a hyperimmune antiserum to FeLV structural proteins. It is hypothesized that FOCMA may actually be a family of antigens, not all of which cross-react with FeSV polyprotein antigens. (21 Refs)

55. DIFFERENTIAL EXPRESSION OF MURINE LEUKEMIA ANTIGEN ON L1210 PARENTAL AND DRUG-RESISTANT SUBLINES.

Strzadala L, Opolski A, Radzikowski C, Mihich E
Inst. Immunology and Experimental Therapy, Czerska 12, 53-114, Wroclaw, Poland
Cancer Res; 41(12):4934-4937 1981

The differential expression of surface antigens on L1210 leukemia DBA/2 and drug-resistant L1210 sublines was investigated. In direct cytotoxic test, the anti-L1210/v alloantiserum reacted more strongly with subline cells than with parental cells. Absorption of the antiserum with Gross cellular surface antigen-positive AKR leukemia (AKSL-4) cells led to a much greater difference in this reactivity. Quantitative absorption experiments revealed that the drug-resistant sublines had 5x higher absorption capacity than did the parental line. After complete absorption of antibodies against murine leukemia virus-related antigens, the anti-L1210/v alloantiserum still

reacted with L1210 cells. This cytotoxicity cou ld be removed after absorption with C3H mammary tumor (MAC-1) cells but not with normal C3H lymphocytes. These results provide evidence that the major cytotoxic activity of the antiserum against L1210 and L1210 subline cells was due to antibodies against murine mammary tumor virus-related antigen and that the drug-resistant sublines of leukemia L1210 have higher quantitative expression of mammary leukemia antigens. (Author abstract) (15 Refs)

56. RETROVIRUS P30-RELATED ANTIGEN IN HUMAN SYNCYTIOTROPHOBLASTS AND IGG ANTIBODIES IN CORD-BLOOD SERA.

Suni J, Wahlstrom T, Vaheri A
Dept. Virology, Univ. Helsinki, 00290 Helsinki 29, Finland
Int J Cancer; 28(5):559-566 1981

Sensitive immunological techniques were used to detect retrovirus markers in human pregnancy. A total of 1,540 human cord-blood sera were tested for retrovirus-reactive IgG antibodies using solid-phase enzyme immunoassay and purified RD114 virus as antigen. Of these, 118 (7.7%) sera were positive. Blocking assays with specific animal anti-p30 sera, use of control antigen, and electrophoretic protein experiments combined with immunological detection indicated that the human antibodies reacted specifically with the p30 protein. The occurrence of antibodies in cord-blood serum had a highly significant correlation to complications during pregnancy and also correlated to the number of previous absorptions and stillbirths. When goat anti-RD 114 p30 serum was used in the peroxidase-anti-peroxidase tissue staining procedure, p30-related antigen was detected in sections of all placental specimens (early and term pregnancies, blighted ova, hydatidiform moles, destructive moles and choriocarcinomas). However, in each case only syncytiotrophoblastic cells were positive. These findings, supplemented with different types of blocking tests, lead us to conclude that retrovirus p30-related antigen is selectively expressed in the highly differentiated syncytiotrophoblasts, which in the normal placenta are directly exposed to maternal blood. It is suggested that retrovirus-reactive antibodies may represent an autoimmune-like immune response to the p30-related syncytiotrophoblast antigen escaping during cellular damage. (Author abstract) (32 Refs)

57. CHARACTERIZATION OF ANTIGENS IN SSV NONPRODUCER CELLS.

Thiel HJ, Matthews T, Broughton E, Butchko A, Bolognesi D
Dept. Surgery, Medical Center, Duke Univ., Durham, NC, 27710
Haematol Blood Transfus; 26:520-523 1981

In an attempt to identify putative transformation specific information coded by simian sarcoma virus (SSV), goat cells nonproductively transformed by SSV (SSV-NP) were isolated and inoculated several times as live cells into the same goat. The resulting hyperimmune serum (SSV-NP serum) was reacted in radioimmunoprecipitation against different transformed and nontransformed cell l ines. After labeling SSV-NP cells with 3H-glucosamine and 35S-cysteine using a 7 hr pulse followed by a 14 hr chase, the respective tissue culture supernatants were immunoprecipitated with SSV-NP serum. The SSV-NP serum reacted specifically with two different molecules in SSV-NP cells, a SSV transformation-specific glycoprotein (SSV TrS-gp) and p65, which probably represents a modified gag-precursor. (7 Refs)

58. RECEPTOR MEDIATED LEUKEMOGENESIS (MEETING ABSTRACT).

Weissmar IL, McGrath MS, Jerabek L
Stanford University, Stanford, CA
Exp Hematol; 9(Suppl9):120 1981

We have proposed an unusual hypothesis for a mechanism by which slowly transforming retroviruses might cause T and B cell leukemia: such viruses bear on their surface envelope glycoprotein. We propose that these retroviruses bind via their envelopes to antigen specific receptors on T and B cells, trigger proliferation of these cells in much the same way that antigen binding to normal T and B lymphocytes trigger proliferation, and infect these cells in a way that leads to continued production of antigen by receptor bearing lymphocytes. This could lead to unlimited proliferation by these cells in response to the antigen they produce. In this case the viral oncogene would be the gene coding for the envelope glycoprotein. We have demonstrated that each cloned T and B lymphoma indeed bears on its surface receptors specific for particular virus which is produced by them. Interruption of receptor binding to lymphoma cells prevents their further proliferation, and this usually can be reversed by addition of high concentrations of the specific binding virus. These receptors are present in vivo on T lymphoma cells and not on the surrounding thymocytes which predominate in the preleukemic period. Current work implicates the receptor molecules on B cell lymphomas to be either their surface immunoglobulins, or molecules which preferentially associate with such surface immunoglobulin. (no Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

59. STUDIES OF TARGET CELL RECOGNITION BY CYTOTOXIC T LYMPHOCYTES.

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Diss Abstr Int [B]; 42(4):1384-B 1981

Cytotoxic T lymphocytes (CTL) generated during a murine sarcoma virus (MSV) infection have been found to be specific for both viral and H-2 antigens. Thus, in order for a target cell to be killed, it must express the same H-2 antigens as the CTL (H-2 restriction). Specifically, CTL recovered from primary MSV-induced tumors and spleens of H-2b mice are specific for the H-2Db molecule recognized in association with a viral antigen shared by the Friend, Moloney and Rauscher (FMR) viruses. The H-2Db specificity has now been studied using a mutant cell line. A Friend virus-induced tumor cell line originating from a hete rozygous H-2b/H-2d mouse was mutagenized with ethyl methanesulfonate (EMS). These cells were then treated with a hybridoma antibody directed against the H-2Db molecule in the presence of rabbit complement. The surviving cells were no longer susceptible to the hybridoma antibody but were still lysed with conventional anti-H-2Db alloantiserum plus complement. Data obtained by sequential immunoprecipitation followed by gel electrophoresis indicate that both antisera recognized the same molecule. When the mutant cells were used as targets for H-2DbFMR specific CTL, the amount of cell lysis, compared to that seen with the nonmutant parent cells, was drastically decreased. However, they remain susceptible to allogeneic CTL raised against the H-2Db molecule. The mutant cells also did not differ from the

parent cells in their level of viral antigen expression. Comparative tryptic peptide maps indicated that the H-2Db molecules from the parental and mutant cells were similar but not identical. These studies suggest that a possible mechanism of escape by virus-infected cells from destruction by CTL might be alteration by somatic mutation of the Class I H-2 glycoprotein(s) that must be recognized by the CTL in order for them to be effective. (no Refs)

60. INDUCTION OF TARGET ANTIGENS AND CONVERSION TO SUSCEPTIBLE PHENOTYPE OF NK-CELL-RESISTANT LYMPHOID CELL LINE.

Clark EA, Sturge JC, Falk LA
Regional Primate Res. Center, Univ. Washington, Seattle, WA, 98195
Int J Cancer; 28(5):647-654 1981

Two autologous Herpesvirus papio producer lymphoid cell lines and one autologous non-producer line were compared for susceptibility to natural killer (NK) cell-mediated lysis. The non-producer cell line, 26CB-1, was more resistant to NK cell killing compared to one viral producer counterpart 13CB-I, but equally resistant when compared to another, 8CB-I. Treatment with chemical agents that affect differentiation or activate the viral cycle, including n-butyrate, IuDR, 5-azacytidine and tunicamycin, increased the susceptibility to killing of the non-producer line but had less effect on the 13CB-I producer line. The increase in susceptibility was due to induction of new target antigens: activated 26CB-I cells were more effective at inhibiting NK-cell-mediated lysis and were bound by more NK cells than untreated control cells. The expression of NK target structures may be related to the differentiated state rather than to the viral production status of target cells. (Author abstract) (43 Refs)

61. DETERMINANTS OF SUSCEPTIBILITY AND RESISTANCE TO FELINE LEUKEMIA VIRUS INFECTION. I. ROLE OF MACROPHAGES.

Hoover EA, Rojko JL, Wilson PL, Olsen RG
Dept. Veterinary Pathobiology, Ohio State Univ., 1925 Coffey Rd., Columbus, OH, 43210
JNCI; 67(4):889-898 1981

The role of autochthonous peritoneal feline macrophages (Mtheta) in the age-rela ted resistance of cats to feline leukemia virus (FeLV) was investigated by a study of the functional properties and FeLV susceptibility of Mtheta from kittens and adult cats and the effect of hydrocortisone (HC) and silica on Mtheta-FeLV interactions. Although the phagocytic functions of isolated Mtheta from kittens and adults were equivalent, the mean FeLV susceptibility of Mtheta from kittens was 5x that of Mtheta from adult cats, thus establishing a direct correlation between the age-related susceptibility of cats and Mtheta from cats to FeLV. Mtheta of viremic cats were found to be infected with FeLV in vivo; virus titers were slightly higher than those obtained after in vitro infection of Mtheta. Mtheta from cats that had experienced regressive FeLV infection were not significantly more resistant to FeLV infection in vitro than were Mtheta from naive adult specific-pathogen-free cats. HC, which has been shown to enhance the in vivo FeLV susceptibility of cats, also enhanced the permissiveness of Mtheta from cats to FeLV in vitro (600-fold for Mtheta from adult cats and 200-fold for Mtheta) from kittens. Mtheta permissiveness to FeLV was highly sensitive to HC and occurred in Mtheta infected in vivo or in vitro. In parallel with the effect of HC on the natural resistance of cats to FeLV, administration of silica before virus inoculation also markedly enhanced the FeLV susceptibility of adult cats. Silica was toxic for isolated Mtheta but not for lymphocytes in vitro, and silica produced monocytopenia and neutrophilia, delayed skin allograft rejection, and augmented feline oncovirus-associated cell membrane antigen antibody responses in vivo. These experiments indicate that Mtheta were linked to the natural resistance of cats to FeLV and that the temporary elimination of Mtheta functions (eg, by silica) and/or the conversion of the Mtheta-FeLV relationship from a nonpermissive to a permissive state (eg, by corticosteroids) resulted in failure of early virus containment, in persistent virus amplification in hemolymphatic tissues, and in subsequent FeLV-related proliferative or antiproliferative disease. (Author abstract) (72 Refs)

62. CYTOTOXIC T CELL RECOGNITION OF EPSTEIN-BARR VIRUS-INFECTED B CELLS. I. SPECIFICITY AND HLA RESTRICTION OF EFFECTOR CELLS REACTIVATED IN VITRO.

Moss DJ, Wallace LE, Rickinson AB, Epstein MA
(c/o Rickinson) Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Eur J Immunol; 11(9):686-693 1981

The experiments show that the phenomenon of regression, seen exclusively in Epstein-Barr (EB) virus-infected cultures of mononuclear cells from EB virus antibody-positive donors, is mediated by cytotoxic T cells reactivated in vitro and specifically recognizing an EB virus-induced lymphocyte-detected membrane antigen LYDMA. Thus, effector T cells from regressing cultures kill autologous EB virus- transformed cells but not autologous pokeweed mitogen-stimulated lymphoblasts nor any of a range of EB virus genome-negative human hemopoietic cell lines (K562, HSB2, BJAB, EB4) particularly sensitive to nonspecific natural killer-like activities. Moreover, these reactivated effector cells exhibit classical HLA restriction of target cell recognition; in a survey of 14 effector cell donors, preferential lysis of the autologous virus-transformed line was a consistent feature, while the relative degree of lysis of allogeneic lines was in general directly related to the number of HLA-A and B antigens shared between effector and target cells. The pattern of reactivity shown by effector T cell preparations from any one donor was strikingly reproducible, and the results from a number of donors revealed differences between particular HLA-A and B antigens with respect to the level of EB virus-specific killing which was associated with sharing through these determinants. (Author abstract) (52 Refs)

63. CYTOTOXIC T CELL RECOGNITION OF EPSTEIN-BARR VIRUS-INFECTED B CELLS. II. BLOCKING STUDIES WITH MONOCLONAL ANTIBODIES TO HLA DETERMINANTS.

Wallace LE, Moss DJ, Rickinson AB, McMichael AJ, Epstein MA
(c/o Rickinson) Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Eur J Immunol; 11(9):694-699 1981

Monoclonal antibodies specifically binding common determinants on all HLA-A, B and C antigen molecules blocked the lysis of EB virus-transformed target cells by EB virus-specific cytotoxic T cells reactivated in vitro. Blocking was mediated through binding of the antibodies to the target rather than to the effector cells and was max (75 to 85% inhibition of lysis) at saturating antibody concentrations. A similar blocking effect was also shown by a monoclonal antibody binding to beta2-microglobulin, a molecule physically associated with HLA-A, B and C antigens on the target cell surface, but not by a monoclonal antibody binding to the non-HLA-associated WBC-

common antigen. Saturating concentrations of monoclonal antibodies specific for common determinants on all HLA-DRw antigen molecules either had no effect at all upon EB virus-specific T cell cytotoxicity or caused a slight, but nonspecific, inhibition. The results demonstrate unequivocally that HLA-A, B and C antigens on the target cell surface are indeed the polymorphic elements which impose genetic restriction upon EB virus-specific cytotoxicity T cell function. (Author abstract) (32 Refs)

64. CHANGES IN THE APPEARANCE OF THE KILLER T CELLS AGAINST CELLS INFECTED WITH EPSTEIN-BARR (EB) VIRUS DUE TO CHANGES IN PROPERTY OF THE INDUCTION-STIMULATING ANTIGEN (MEETING ABSTRACT).

Yoshimura N, Yada J
Dept. Pediatrics, Tokyo Medical and Dental Univ., Sch. Medicine, Bunkyo-ku, Tokyo 113, Japan
Proceedings of the 9th Annual Meeting of Japan Society of Clinical Immunology he ld in Tokyo, 13-15 June, 1981. Japan Society of Clinical Immunology, Saitama Pref. 350-04, Japan, 239 pp., 1981.

Adult human lymphocytes were infected with EB virus derived from B95-8 (cell-line) to establish the culture of B cells which were used as the target. The lymphocytes were stimulated by mitomycin C (MMC)-treated B cells obtained from the same lymphocytes. The killer T cells that appeared were allowed to react with 51-Cr-labeled cells of the same established line, to determine their cytotoxicity. The change in the induction of the regulatory cells of the killer, which is caused by changing the method of adding the antigen was determined. The appearance of killer T cells decreased when heat-treated cells (I region-associated (Ia) antigen is reduced) were used for sensitization. The appearance of the killer T cells was restored when the T cells that had been stimulated by the MMC-treated cell line cells were treated with MMC and the two kinds of cells were added together. Therefore, helper T cells induced by EB virus-infected cells having Ia antigens were considered a requisite for the appearance of killer T cells. It was difficult to induce helper cells by the antigen solubilized by 3 M KCl in the absence of macrophages. Suppressor T cells were induced when heat-treated stimulant cells were used. (no Refs) (In JPN)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

65. CONVERSION OF HERPETIC LESIONS TO MALIGNANCY BY ULTRAVIOLET EXPOSURE AND PROMOTER APPLICATION.

Burns JC, Murray BK
Dept. Oral Pathology, Dept. Microbiology, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA, 23298
J Gen Virol; 55(part2):305-313 1981

Many lines of evidence exist associating herpes simplex virus (HSV) with the development of carcinoma, but much of this evidence in anecdotal or associative in nature and does not prove a cause and effect. The purpose of this research was to investigate the oncogenic potential of HSV Type 2 (HSV-2) in vivo. A mouse model for lip carcinogenesis was designed to combine HSV-2 infection, UV exposure and tetradecanoylphorbol-acetate (TPA) application. HSV-2 inoculation on to abraded mouse lips was capable of causing vesicular ulcerative lesions which healed completely after 10 to 14 days. UV irradiation of the HSV lesion site daily for 6 min at 42 ergs/mm2/s on days 3 to 6 post-infection caused hyperkeratosis, acanthosis and dysplasia to develop in several lips; while the same UV exposure by itself failed to alter the histologic appearance. The addition of repeated TPA application to the HSV + UV regimen promoted tumor emergence. Thirty-two of 156 Balb/c mice developed tumors. Although the majority were papillomas, six were squamous cell carcinomas. These tumor-bearing mice had increased HSV-specific antibody titers. HSV antigens were shown to be present in outgrowths from explanted tumors as well as in tumor biopsies by immunoperoxidase staining with HSV-specific antisera. It is suggested that the in vivo UV-irradiated HSV acted as an inducer and TPA as the promoter, analogous to the classical two-stage carcinogenesis model. (Author abstract) (29 Refs)

66. THE PRESENCE OF SV40 T-ANTIGEN IS NOT REQUIRED FOR CYTOCHALASIN B-INDUCED MULTINUCLEATION.

Connor CG, Brownstein BL
Dept. Biology, Temple Univ., Philadelphia, PA, 19122
Cell Biol Int Rep; 5(11):1027-1031 1981

Two different rat liver epithelial cell lines sensitive for SV40 transformation were studied to determine if T-antigen is responsible for the uncontrolled nuclear division found in such cells treated with cytochalasin B. Since multinucleation was found at temperatures at which T-antigen was not immunologically detectable, T-antigen is not necessary for cytochalasin B-induced multinucleation. (15 Refs)

67. ADRIAMYCIN IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC) (MEETING ABSTRACT).

Gennari L, Tommasini MA, Orefice S, Bignami AM, Maggi CA, Colucci G, Colombo M
Istituto Nazionale dei Tumori, Milan, Italy
Gastroenterology; 80(5,part2):1333 1981

To study whether the route of drug administration and coexisting cirrhosis may influence the response to adryamicin (ADM) of patients with unresectable HCC, we randomly treated 33 consecutive patients (M:F equals 4, mean age 60 yr, range 38-81 yr) by giving ADM either iv or through intraceliac catheter (ia), according to Seldinger technique. Response to therapy was evaluated comparing treated patient's survival with that of 68 sex, age and tumor matched, untreated patients with unresectable HCC. Selective responses in the treatment groups were related to cirrhosis and route-of administration, but were independent from hepatitis B surface antigen (HBsAg) seropositivity and pretreatment levels of alphafetoprotein. ADM increased the survival and improved life quality in cirrhotics treated iv and in non-cirrhotics treated ia. The longest survival was observed in non-cirrhotic patients treated by ia ADM. On the contrary, no favorable response was observed in cirrhotics treated ia nor in non-cirrhotics treated iv. In conclusion, ADM may represent an effective therapy for unresectable HCC, provided that patients are selected for the route of drug administration on the basis of coexisting cirrhosis. (no Refs)

68. ENHANCEMENT OF CYTOTOXICITY OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES BY INTERFERON.

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Dept. Microbiology, Hokkaido Univ. Sch. Medicine, Kita-ku, Sapporo, Hokkaido 060, Japan

Microbiol Immunol; 25(8):837-845 1981

The usefulness of the human lung carcinoma cell line (Pc-10) and Pc-10 cells persistently infected with mumps virus (Pc-10/MpV) as target cells for analyzing the relationship between alpha-i nterferon (IFN-alpha) and human natural killer (NK) activity was examined. Both Pc-10 and Pc-10/MpV were found to be useful as target cells. Pc-10/MpV were lysed more efficiently that uninfected Pc-10 cells by the same lymphocyte subpopulation, namely non-T, non-B cells, which correspond in part to NK cells. Human peripheral blood mononuclear leukocytes (PBML) were obtained from healthy donors who had antibody against mumps virus in their blood and were sensitive to mumps virus antigens in the skin reaction; no T cell-dependent cytotoxicity for Pc-10/MpV cells was observed. NK activity and the production of IFN/alpha in human PBML could not be dissociated, since anti-IFN-alpha suppressed the NK activity of PBML. Augmentation of the cytotoxicity of PBML by IFN-alpha was detectable within 2 hr of incubation. The effect of IFN-alpha on the augmentation of the cytotoxicity of human PBML for Pc-10 was dependent on the dose from 0.8-60 IU/ml. No difference between the augmentation of the cytotoxicity of human PBML by gamma-interferon and IFN/alpha was observed. (39 Refs)

69. EFFECT OF VINBLASTINE ON DISTRIBUTION OF MURINE LEUKEMIA VIRUS-DERIVED MEMBRANE-ASSOCIATED ANTIGENS.

Satake M, McMillan PN, Luftig RB

Dept. Microbiology and Immunology, Univ. South Carolina Sch. Medicine, Columbia, SC, 29208

Proc Natl Acad Sci USA; 78(10):6266-6270 1981

The effect of vinblastine on the distribution of murine leukemia virus-derived membrane-associated antigens was examined by using the indirect immunofluorescence of 3.7% formaldehyde-fixed MJD-54 (Moloney murine leukemia virus-infected) cells. On fixed, non-drug-treated cells, p30 antigen was distributed homogeneously and diffusely over the cell membrane. When cells were incubated with 10 uM vinblastine for 1 hr before fixation, the distribution of p30 antigen was greatly changed, fluorescence now being collected into poles (cap-like formation). In contrast to this distribution pattern for p30 antigen, gp70 antigen was distributed in a micropunctate pattern on the cell surface, with or without vinblastine pretreatment. These observations indicate that the distribution patterns of p30 and gp70 membrane antigens are completely different and that they are differently controlled by cytoplasmic microtubules. In addition, because the p30 membrane antigen visualized in these studies most likely represents viral Pr65gag precursor molecules which are localized directly under and associated with the plasma membrane, these results suggest that, under special conditions of fixation, it is possible to obtain a cap-like phenomenon for cytoplasmic (internal) membrane-oriented proteins. (Author abstract) (24 Refs)

70. INHIBITION OF MURINE LEUKEMIA VIRUSES IN VITRO BY PHOSPHONOFORMATE (MEETING ABSTRACT).

Varnier OE, Repetto CM, Raffanti SP

Institute of Microbiology, Genova, Italy

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

It has recently been found that low concentrations of phosphonoformate (PFA) have a high antiviral activity. PFA inhibits herpesvirus and hepatitis B DNA polymerases and influenza RNA polymerase. It also acts as a specific inhibitor of reverse transcriptase of several mammalian retroviruses at concentrations non inhibitory to macromolecular synthesis and cell proliferation. We have investigated the effect of PFA on the infection, replication and viral antigen expression of some murine leukemia viruses (MuLV). Minimal concentrations of PFA (100-500 uM) reduce by 80-100% the XC plaque forming ability of Friend, Moloney and AKR strains of MuLV, at different multiplicities of infection. These results are substantiated by the progeny levels detected in these infected cell cultures. The viral titers were reduced up to 450 fold in the presence of PFA, with respect to controls. In this report we present further evidence for the specific activity of PFA on virus replication, using murine retroviruses as a model system useful for the understanding of the mechanism of action of this new antiviral drug. (no Refs)

OTHER RELATED STUDIES

71. ROLE OF ONCOFETAL ANTIGEN IN REGULATION OF CELLULAR IMMUNITY DURING PREGNANCY AND TUMOR DEVELOPMENT (MEETING ABSTRACT).

Coggin JH

Department of Microbiology/Immunology, University of South Alabama, Mobile, AL, 36688

Oncodev Biol Med; AbstractsBook,1:38 1981

Tumor cells of the hamster and mouse induced by oncogenic DNA viruses carry cell surface antigens which are identical to those which appear temporally during fetal development in both species. We have established that immune regulation mediated by suppressor T lymphocytes (Ts) occurs during pregnancy and is directed against oncofetal antigen (OFA) determinants present on fetus and tumor cells. These Ts cells prevent cell mediated cytotoxic lymphocytes from killing fetal cells expressing OFA and similarly act against the killing of OFA positive tumor cells. A serum component, mediating non-specific suppression of Concanavalin A stimulation of hamster and mouse splenocytes can also be detected. The time course of the development of T suppressor cells which play an important role in immune regulation during pregnancy and a similar role during the development of OFA expressing tumor cells during early oncology are described. OFA can be released from fetal cell surfaces and has been characterized. (no Refs)

72. ANTIGENS REACTING WITH HETEROANTISERA AND MONOCLONAL ANTIBODIES ON THE SURFACE OF LEUKEMIA AND LYMPHOMA CELL LINES AND CELL HYBRIDS (MEETING ABSTRACT).

Goldblum N, Mitrani S, Billard C, Galili N, Martyre MC, Kayibanda M, Mishal Z, Hercend T, Goutner A, Ber R, Boucheix C, Rosenfeld C
Department of Virology, Hebrew University-Hadassah Medical School, Jerusalem, Israel
Exp Hematol; 9(Suppl9):164 1981

Several human leukemia and lymphoma cell lines were studied for the presence of cALL antigen. In addition to an absorbed rabbit heteroantiserum to acute lymphocytic leukemia (cALL), a 'more specific' monoclonal antibody was used. Certain cell lines were found equally reactive with both cALL and J-5. Other cell lines, such as DG-75, a non-Epstein-Barr virus (EBV) genome carrying Burkitt lymphoma line and HD-Mar, a T-cell leukemia cell, were highly reactive with cALL but were either completely (DG-75) or partially (HD-Mar) negative with J-5. A hybrid cell line, Hu/Dut, prepared by fusing a Daudi with a human epithelial cell line U, reacted neither with cALL nor with J-5, indicating that the expression of the(se) glycoprotein(s) on the surface membrane is completely inhibited in this hybrid. IgM and Kappa, as well as Ia which are present on the surface of all parent Daudi cells were also completely absent in the hybrid. Hu/Dut carries, however, EBV genome(s), as indicated by a highly positive reaction for the intranuclear EBNA antigen. Four T-cell lines isolated by us from T-cell leukemic patients were studied for E-rosette formation with SRBC, reaction with an anti-HuTLA rabbit antiserum and with monoclonal antisera of the OKT and LEU series. Varying reactivities with the different reagents were observed indicating enormous heterogeneity of the leukemic T cell isolates. (1 Ref)

73. IMMUNODEFICIENCIES IN HODGKIN'S DISEASE. PART I: T CELL-MEDIATED IMMUNITY.

Gupta S
Clinical Immunology Service, Sloan-Kettering Inst., New York, NY
Clin Bull; 11(2):58-65 1981

The association between Hodgkin's disease and immunodeficiency states is reviewed. Immunodeficiencies may predispose patients with Hodgkin's disease to a second neoplasm and to increased risk of infectious complications, especially viral and fungal (eg herpes zoster and cryptococcosis). Both in vivo and in vitro T cell-mediated immune responses in patients with various stages of Hodgkin's disease are discussed, including delayed type hypersensitivity, homograft rejection, lymphocyte response to soluble antigens and to mitogens and allo-antigens, analysis of T cells and T cell subsets, and cytotoxic response and mechanisms responsible for T cell-mediated immunodeficiencies. The role played by splenectomy in treatment of Hodgkin's disease is discussed. (71 Refs)

74. A POSSIBLE ROLE OF THE NUCLEUS IN CYTOCHALASIN B-INDUCED CAPPING.

Otteskog P, Ege T, Sundqvist KG
Dept. Periodontology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
Exp Cell Res; 136(1):203-213 1981

The possible influence of the nucleus on Cytochalasin B (CB)-induced capping of antibodies to surface antigens on L cells SV40-3T3 and NRK La 334 cells was studied. The cap formation induced by CB, was generally localized opposite the nucleus which was displaced against the cell periphery. To be able to observe the nuclear membrane in relation to the capping process we have taken advantage of an antiserum specific for antigens in the nuclear membrane but lacking reactivity to the plasma membrane and intranuclear antigens. This approach indicated that the CB-induced capping caused an accumulation of nuclear membrane antigens in the area of the nucleus facing the cap. The CB-induced local accumulation of nuclear membrane antigens required intact cells and could not be induced by binding of antibodies to the nuclear membrane followed by exposure to CB. Whatever the basis for the CB-induced altered reactivity of the anti-nuclear membrane antibodies (folding of the nuclear periphery, for example) this result indicated that the nuclear membrane was affected by CB capping. The possible role of the nucleus in the CB-induced capping process was further investigated in enucleated cells. The results obtained indicate that such cells both when enucleated in suspension and adherent to a surface did not exhibit CB capping. This disappearance of CB capping probably did not reflect decreased cell viability, previous exposure of the cells to CB during the enucleation procedure or a decreased capacity of the enucleated cells to bind CB. (Author abstract) (25 Refs)

75. HUMAN MELANOMA-ASSOCIATED ANTIGENS; IMMUNOCHEMICAL AND MOLECULAR PROFILE.

Reisfeld RA, Galloway DR, Morgan AC, Walker LE, Bumol TF
Scripps Clinic and Res. Foundation, La Jolla, CA
Cancer Bull; 33(5):211-218 1981

Some of the immunochemical approaches taken in the authors' laboratory to isolate and characterize two human melanoma-associated antigens utilizing specific polyclonal and monoclonal antibodies are described. Analysis of cellular proteins released into the surrounding culture of several human melanoma cells lines indicated three major components detected by polyclonal antimelanoma xenoantisera with mol wt of 260K (260,000), 240K and 100K. The 240K component has been identified as fibronectin. The 100K component is found in spent media of both melanoma and carcinoma cell lines. The 100K and 260K dalton antigens which have affinity for specific lectins and metabolic radiolabeling with sugars strongly suggest they were glycoproteins. Other studies are reported on the use of monoclonal antibody for structural characterization, production of monoclonal antibody, subunit composition of 100K and 250K dalton melanoma antigens, and functional properties. It is apparent that the two melanoma-associated antigens of 100K and 250K dalton, defined immunochemically by monoclonal antibody, are likely to play a key role in the elicitation of host im mune responses to malignant melanoma. Furthermore, it appears that changes in intracellular transport, glycosylation, and cell-surface expression of these two markers may be associated with neoplastic transformation. (12 Refs)

76. ANATOMIC PATHOLOGY: A NEW ENZYME IMMUNOLECTIN TISSUE STAIN.

Robb JA
Dept. Pathology, Green Hosp. Scripps Clinic, La Jolla, CA
Diagn Med; 4(7):87-89,92-95 1981

An enzyme-linked immunolectin histochemical staining technique for identification of disease processes in tissue samples is described. The method uses a glucose oxidase-avidin-biotin (GAB) antibody complex to amplify primary antigen-antibody interactions. GAB assay has high sensitivity and is free of background interference. Antigens can be detected in any location or amount. The assay is easily reproduced and does not require extensive training of pathologists. Applications include

the detection of normal cellular products (including keratin, anterior pituitary hormones, and ABO blood group antigens), infectious agents, and lymphocyte surface markers. GAB assay makes it possible to differentiate between various types of herpetoviruses and may eventually be useful for detection of tumor-specific antigens. The method can detect many, if not all, antigens in formalin-fixed tissue specimens. (11 Refs)

77. A HYPOTHESIS ON THE ETIOLOGY OF ADULT T-CELL LEUKEMIA/LYMPHOMA.

Tajima K, Tominaga S, Shimizu H, Suchi T
Div. Epidemiology, Aichi Cancer Center Res. Inst., 81-1159 Kanokoden, Tashiro-cho, Chikusa-ku, Nagoya 464, Japan
Gan; 72(5):684-691 1981

The results of the nationwide survey performed by the T- and B-cell Malignancy Study Group revealed that adult T-cell leukemia/lymphoma (ATLL) was prevalent in limited zones in Kyushu, mainly in coastal areas, warm in winter and humid in summer. It was found that the geographical distribution of filariasis was very similar to that of ATLL. It is known that filariasis affects lymphatic vessels and results in several lymphoreticular ailments, and microfilaria is transmitted by mosquitoes infected with some kinds of not yet fully identified viruses. From analyses of the time trends of the av wt and height of school children by prefecture, it is suggested that the nutritional condition of inhabitants in Kyushu might have been poorer than that of inhabitants of other areas in Japan, especially in the past. In order to elucidate the etiology of ATLL, relevant geographic-pathological information and other related information was accumulated and an etiological hypothesis was formulated. It was hypothesized that repeated exposure to filarial antigen and some viruses might have played an important role in the etiology of ATLL and that undernutrition had also contributed to the progression of ATLL. (Author abstract) (31 Refs)

78. CLONED HUMAN T CELLS WITH NATURAL KILLER ACTIVITY: SPECIFICITY, CELL SURFACE MAR KERS AND RELATIONSHIP TO GRAFT VERSUS HOST REACTIVITY (MEETING ABSTRACT).

Wernet P, Hadam M, Ziegler A, Pawelec G
Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany
Exp Hematol; 9(Suppl9):49 1981

Human lymphocytes alloactivated in mixed WBC cultures (MLC) display a variety of different immunological functions in vitro including natural killer (NK) activity. Cloning by limiting dilution and propagation of cloned cells in conditioned medium was followed by assay on several human NK sensitive targets in order to analyze whether target specificities segregate upon cloning. Such NK populations strongly kill K 562, MOLT 4 and RPMI 1301 cell line blasts as well as cells from the leukemic T cell line HSB 2, but not target cells from the Epstein Barr virus (EBV) transformed B cell line of the same donor (SB) in the standard 51Cr release assay. NK cells may have receptors which recognize identical antigens on all NK-sensitive targets or may posses multiple receptors for different target specificities. Surface marker profiles of cloned NK cells determined in indirect immunofluorescence with a set of 48 well defined monoclonal antibodies displayed certain classical T cell characteristics as well as NK specific determinants. These cells in addition can exert a very effective suppression of lymphocyte stimulation which is apparently not brought about by killing. This particular NK cell type was identified by surface markers in several patients with graft versus host reactivity following successful allogeneic bone marrow transplantation. (no Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. DEPRESSED IMMUNITY AND THE DEVELOPMENT OF CANCER.

Penn I
Dept. Surgery, Univ. Colorado Health Sciences Center, 1055 Clermont St., Denver, CO, 80220
Clin Exp Immunol; 46(3):459-474 1981

Epidemiological, clinical, and experimental studies of depressed immunity and cancer are reviewed. Topics include transplantation of tumors, cancer in patients with naturally occurring immunodeficiency disorders, de novo cancer in organ transplant recipients, and cancer in uremic patients. Patients

HE 20. 3173/2:

with autoimmune and other diseases treated with immunosuppressive agents have increased cancer incidence. Second cancers, particularly leukemias, are more frequent in patients treated with chemo- and radiotherapy. Disturbances in immunity as causes of cancer are presented; immune surveillance, immune stimulation, chronic antigenic stimulation, defective immunoregulation, spontaneous regression of lymphomas, interferons, oncogenic viruses, oncogenic and co-oncogenic effects of immunosuppressive and cancer therapeutic agents, and other potentially oncogenic treatments (UV and arsenic for psoriasis) are discussed. Animals and patients vary in their susceptibility to oncogenic stimuli. Evidence suggests that the immune system plays a key role in host defense against cancer, but many unanswered questions remain. (149 Refs)

2. GENITAL CANCER AND VIRUSES.

Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

Current data suggesting an association between viruses and genital cancer are reviewed. The main emphasis is on the relationship between herpes simples virus Type 2 (HSV-2) and cervical cancer. Seroepidemiological studies are presented along with emphasis on HSV-transforming and oncogenic potential. Although the evidence is indirect, it is highly suggestive. HSV-2 has the oncogenic potential to produce neoplastic disease in animals. The ability of HSV-2 to transform cells in vitro and for transformed cells to produce tumors in vivo is presently the most direct evidence for oncogenic potential. In vivo experiments, more closely linking HSV-2 and cervical cancer are hampered by the severe cytopathic effect of HSV-2. Evidence associating two other viruses, human cytomegalovirus (CMV) and human papilloma virus (PV), with cervical and prostatic cancer are also discussed. Factors associating CMV with genital cancer include the establishment of persistent infections of the genitourinary tract, transmission by sexual contact, seroepidemiological studies with antibodies and genital cancer, detection of virus particles or virus-specific antigens in genital cancer biopsies, and in vitro transformation studies. Factors associating FV with genital cancer include association with venereal disease, conversion of condylomata acuminata to malignant state, and detection of genital carcinoma within condylomata. (97 Refs)

3. SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS.

Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeld SJ, Gold J, Hassett J, Hirschman SZ, Cunningham-Rundles C, Adelsberg BR, Parham DM, Siegel M, Cunningham-Rundles S, Armstrong D
Mt. Sinai Medical Center, New York, NY, 10029
N Engl J Med; 305(24):1439-1444 1981

Cellular immunodeficiency associated with chronic perianal ulcerative herpes simplex lesions is reported in four homosexual men. Onset of the disease was characterized by malaise, fever, and wt loss. Later infections included cytomegalovirus, Pneumocystis carinii, and Candida albicans. One patient developed Kaposi's sarcoma. Skin anergy, lymphopenia, poor or absent responses to plant lectins and antigens in vitro, and depressed natural killer cell activity against target cells infected with herpes simplex virus were observed. An association may exist between primary cytomegalovirus infection and a particularly prolonged cellular immunodeficiency state. (29 Refs)

4. CLUSTERING OF HEPATITIS B VIRUS INFECTION AND HEPATOCELLULAR CARCINOMA IN A FAMILY.

Gilmore IT, Harrison JM, Parkins RA
Royal Liverpool Hosp., Liverpool L7 8XP, England
J R Soc Med; 74(11):843-845 1981

Family clustering of primary hepatocellular carcinoma (HCC) is well recognized, although rare. One possible reason for such clustering has become apparent since the advent of tests to detect circulating markers of hepatitis B virus infection, and this has been the common etiological factor in three families studied. We report the results of screening a Chinese family following the death of one member who had been found to have HCC associated with hepatitis B surface antigenemia. Four of seven siblings were traced: one had died of HCC 5 yr earlier, and evidence of past or present hepatitis B infection was found in the remaining three, one of whom was also found to have HCC. (Author abstract) (24 Refs)

5. HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS. A PROSPECTIVE STUDY OF 22,707 MEN IN TAIWAN.

Beasley RP, Lin CC, Hwang LY, Chien CS
Univ. Washington Medical Res. Unit, 15-2 Kung Yuan Road, Taipei, Taiwan
Lancet; 2(8256):1129-1133 1981

A prospective general population study of 22,707 Chinese men in Taiwan has shown that the incidence of primary hepatocellular carcinoma (PHC) among carriers of hepatitis B surface antigen (HBsAg) is much higher than among non-carriers (1,158/100,000 vs 5/100,000 during 75,000 man-yr of follow-up). The relative risk is 223. PHC and cirrhosis accounted for 54.3% of the 105 deaths among HBsAg carriers but accounted for only 1.5% of the 202 deaths among non-carriers. These findings support the hypothesis that hepatitis B virus has a primary role in the etiology of PHC. (Author abstract) (25 Refs)

6. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.

Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

Current evidence on etiology of human cervical neoplasia (CN) was reviewed. Epidemiological factors of possible etiological significance are coitus, marriage, pregnancy, penile factors, syphilis, trichomoniasis, and herpesvirus genitalis (HVG). Seroepidemiologic studies of herpesvirus type 2 (HSV-2) gave indirect evidence of its etiologic role in human CN. Squamous carcinoma of the cervix behaves as a venereal disease. Findings suggest that certain males having venereal diseases may transmit a risk factor for CN by coital contacts. A necessary condition is that certain females are receptive hosts for the putative venereal carcinogen. Risk factor in females is associated with steroid hormone balance (estrogenic hormones). A virion polypeptide AG-4 associated with the active growth phases of CN and a structural component of the HVG, AG-e was identified and isolated. (81 Refs)

7. DETECTION OF NUCLEIC ACID SEQUENCES IN CERVICAL TUMORS.

McDougall JK, Galloway DA, Crum C, Levine R, Richart R, Fenoglio CM
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Gynecol Oncol; 12(2,part2):S42-S55 1981

Our results suggest that HSV RNA is present in abnormal cells of a significant proportion of cervical tissue specimens containing intraepithelial neoplasia and that it is only rarely detected in sections of normal cervical epithelium. A proliferation of atypical basal-type cells and their continued persistence through the more mature upper layers is the first indication of dysplasia and CIN in cervical epithelium, and it is in these proliferating cells that evidence of HSV RNA can be found. The results of localizing an HSV-2 antigen (ICSP 11-12) closely parallel the in situ hybridization results. About 30% of patients with dysplasia (CIN I and II) have detectable antigen. It is interesting to note that the incidence of detectable antigen decreased to 12% in patients with carcinoma in situ, but was demonstrable in 20% of patients who had microinvasive or invasive squamous cell lesions. (Author abstract) (52 Refs)

8. CELLULAR AND HUMORAL IMMUNITY IN HODGKIN'S DISEASE: I. PATIENTS IN CONTINUOUS LONG-TERM REMISSION.

Skovmann-Sorensen O, Schroder H, Moller-Larsen A, Haahr S (c/o Haahr) Inst. Medical Microbiology, Univ. Aarhus, Bartholin Building, DK-8000 Aarhus C, Denmark
Scand J Haematol; 27(3):171-180 1981

Cell-mediated and humoral immunity to herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella zoster virus (VZV) were examined in 37 patients with Hodgkin's disease in continuous long term remission. This group had lower blast-transformation than a matched control group to all three antigens. Patients originally showing B-symptoms had higher transformation to VZV than those with A-symptoms. Patients treated with irradiation only had higher transformation than those treated with either chemotherapy or a combination of chemotherapy and irradiation. There was a clear tendency towards lower transformation in patients having been in remission for 2 yr or less. Phytohemagglutinin (PHA) stimulation gave lower response in the patient group than in the control group. Patients with B-symptoms had lower response than those with A-symptoms. Interferon production was specially impaired in patients with B-symptoms. The patient group had higher CF titers against HSV and CMV while the control group had higher titers against VZV. B-symptom patients had higher titers against VZV than A-symptom patients. It is concluded that HD patients have impaired immune function many years after discontinuation of therapy, but there are certain differences regarding the in vitro immunity within the patient groups. (Author abstract) (17 Refs)

9. 'THE HERPESVIRUS HYPOTHESIS' - ARE KOCH'S POSTULATES SATISFIED?

Aurelian L, Manak MM, McKinlay M, Smith CC, Klacsmann KT, Gupta PK
Dept. Comparative Medicine, Johns Hopkins Medical Inst., Baltimore, MD, 21205
Gynecol Oncol; 12(2,part2):S56-S87 1981

The evidence associating herpes simplex virus Type 2 (HSV-2) with squamous cervical carcinoma is critically reviewed. Thirteen criteria for a causal relationship between a virus and a human cancer are listed and evidence is presented demonstrating that in the case of HSV-2 and cervical cancer these have been fulfilled. The original Koch postulates are discussed from the standpoint of modern concepts of virology. In this context, emphasis is placed on the identification in cervical tumor cells of the viral protein ICP 10/AG-4. This protein is expressed in HSV-2 transformed hamster cells and its expression correlates well with the oncogenic potential of the transformed lines. Consistent with these findings, the expression of ICP 10/AG-4 in cervical cells and the prevalence of the specific antibody that it induces, reflect the progression of the cervical tumor. (Author abstract) (92 Refs)

10. THE SPECTRUM OF EPSTEIN-BARR VIRUS DISEASE.

O'Dell JR
Dept. Internal Medicine, Univ. Nebraska Medical Center, NE
Nebr Med J; 66(12):275-278 1981

History and pathogenesis of infectious mononucleosis (IM), chronic IM, and other lymphoproliferative syndromes caused by Epstein Barr virus (EBV) are discussed. Primary EBV infection occurs primarily during childhood and is usually asymptomatic. Transmission is through oropharyngeal secretion of EBV by a seropositive individual to a seronegative individual. IM usually persists for 25-30 days, but some individuals suffer from chronic IM possibly due to the presence of early antigen-R antibodies. Primary EBV infection that develops during adolescence can lead to x-linked recessive lymphoproliferative syndrome (Duncan's disease) or possibly Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma. (5 Refs)

11. ABNORMAL LYMPHOCYTES IN X-LINKED LYMPHOPROLIFERATIVE SYNDROME.

Seeley J, Sakamoto K, Ip SH, Hansen PW, Purtilo DT
Dept. Pathology, Univ. Massachusetts Medical Sch., Worcester, MA
J Immunol; 127(6):2618-2620 1981

Helper and suppressor T cells (labeled by OKT4 and OKT8 antisera, respectively,) were studied in males with X-linked proliferative syndrome (XLP), and in their mothers (carriers), asymptom atic brothers, maternally related male cousins (males at risk), and sisters (females at risk). Carrier mothers and both females and males at risk had normal mean percentages of OKT4 and OKT8 cells. However, XLP patients showed significantly lower OKT4 and higher OKT8 percentages compared with healthy controls; abnormally low OKT4:OKT8 ratios were expressed by 6/10 patients with hypogammaglobulinemia and/or lymphoma. Abnormally high OKT4:OKT8 ratios were found in several of 13 males at risk. Among the subjects at risk, OKT4:OKT8 ratios tended to be highest in those who had antibodies to Epstein-Barr virus (EBV) viral capsid antigen but not to EBV nuclear antigen. The ratios may useful in evaluating males at risk for XLP even before they become EBV-seropositive. (24 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

12. HERPESVIRUS ANTIGENS AS MARKERS FOR CERVICAL CANCER.

Gupta PK, Aurelian L, Frost JK, Carpenter JM, Klacsmann KT, Rosenshein NB, Tyrer HW
Dept. Pathology, John Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Gynecol Oncol; 12(2,part2):S232-S258 1981

A total of 393 patients representing cervical atypias, cancers, and nonneoplastic disease have been studied. Cellular specimens have been stained with antisera raised against total herpes Type 2 virus (HSV-2) and subfractions labeled crude AG-e, pure AG-e, ICP 12, and ICP 14. Reproducibility, statistical significance, false positive and false negative results, specificity, and sensitivity of the various antisera have been investigated. Correlation of immunocytostaining with Papanicolaou staining has been made. Usefulness of these markers in the detection and diagnosis of premalignant and malignant cervical epithelial changes for mass screening has been discussed. Using crude AG-e, pure AG-e, HSV-2, and HSV-1 antisera in a number of blind studies, no significant differences were found in the reproducibility of results. Observations indicated that a minimum of 30 cells must be analyzed to make data amenable to statistical analysis. Exfoliated cells from 62, 75, 77, and 94% of patients respectively diagnosed as mild, moderate, and marked atypia, and cancer were studied with antisera against total HSV-2. Similar results were observed with antisera against pure AG-e. No patient reacted with anti-AG-e or anti-HSV-1 antiserum in the absence of reactivity to antisera against total HSV-2 antigens. Studies using anti-ICP 12 and -ICP 14 antigens established the wide and specific staining character of anti-HSV-2 antisera. Morphologic preservation of cells by Papanicolaou staining after the FA procedures was considered satisfactory for diagnostic purposes. Our studies indicated the potential usefulness of anti-HSV-2 and anti-AG-e antisera in mass cervical cancer screening programs and cytology automation. (Author abstract) (21 Refs)

13. THE SITE OF INTEGRATION OF THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE IN HUMAN CELLS TRANSFORMED BY AN HSV-1 DNA FRAGMENT.

Kit S, Hazen M, Otsuka H, Qavi H, Trkula D, Dubbs DR
Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX, 77030
Int J Cancer; 28(6):767-776 1981

To analyze the site of integration of the herpes simplex virus Type I (HSV-I) thymidine kinase (TK) gene in biochemically transformed human cells, TK- HeLa(BU25) cells were transformed to the TK+ phenotype by a cloned, 2 kbp PvuII fragment of HSV-1 DNA. The transformed cells [HeLa(BU25)/TF pAGO PP3] were fused with mouse LM(TK-) cells, and human-mouse somatic cell hybrid clones (LH PP3 clones 1, 2, 3, 5 and 6) were isolated in HATG-ouabain selective medium. The HeLa(BU25)/TF pAGO PP3 cells and the LH PP3 hybrid clones expressed HSV-1-specific TK activity and a herpesvirus-associated nuclear antigen, and contained herpesvirus nucleotide sequences. Molecular hybridization experiments were carried out to map the HSV-I and flanking cellular nucleotide sequences in the biochemically transformed cells. TK- revertant subclones isolated by growing the LH PP3 clone 5 cells in BrdUrd (and diphtheria toxin) failed to form colonies in HATG medium, but retained HSV-I nucleotide sequences. Isozyme analyses on 21 gene-enzyme systems representing 21 human chromosomes revealed that all of the LH PP3 clonal lines expressed human hexosaminidase B, which has been assigned to chromosome 5, and all were sensitive to diphtheria toxin, which is also a marker for chromosome 5. Chromosome analyses showed that chromosome 5 was the only human chromosome present in mitoses of LH PP3 clone 5 cells and that human chromosome 5 was present in most of the mitoses of LH PP3 clone 1, 2, 3, and 6 cells. The latter clones also contained 1 or 2 additional human chromosomes in some of the cells. As expected from the molecular hybridization analyses, TK- revertants of LH PP3 clone 5 cells retained portions of chromosome 5 and expressed human hexosaminidase B. The results indicate that HSV-I nucleotide sequences were stably integrated in the biochemically transformed cells, most likely in human chromosome 5. (50 Refs)

14. ANTIGENIC AND STRUCTURAL CONSERVATION OF HERPESVIRUS DNA-BINDING PROTEINS.

Littler E, Yeo J, Killington RA, Purifoy DJ, Powell KL
Dept. Microbiology, Univ. Leeds, Leeds LS2 9JT, England
J Gen Virol; 56(part2):409-419 1981

Previously, we have shown a common antigen of several herpesviruses (pseudorabies virus, equine abortion virus and bovine mammillitis virus) to be antigenically related to the major DNA-binding proteins of herpes simplex virus Types 1 and 2. In this study we have purified the cross-reacting polypeptide from cells infected with pseudorabies virus, equine abortion virus and bovine mammillitis virus and shown the cross-reacting protein to be a major DNA-binding protein for each virus. Tryptic peptide analysis of the cross-reacting DNA-binding proteins of all five viruses has shown structural similarities. The proteins thus were shown to share common antigenic sites, to have similar biological properties and to have a highly conserved amino acid sequence. This unexpected similarity between proteins from diverse herpesviruses suggests an essential and fundamental role of the major DNA-binding protein in herpes virus replication. (Author abstract) (28 Refs)

15. IDENTIFICATION OF ANTIGENIC DETERMINANTS UNIQUE TO THE SURFACES OF CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Kintner C, Sugden B
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Nature; 294(5840):458-460 1981

Four monoclonal antibodies (anti-EBVCS) that detect antigenic determinants unique to the surfaces of Epstein-Barr virus (EBV)-transformed cells but are not associated with virus production were isolated. Cell lines transformed in vitro or those transformed in vivo but not associated with Burkitt's lymphoma bound anti-EBVCS strongly, whereas cell lines from patients with Burkitt's lymphoma bound them at intermediate levels or not at all. When untreated lymphocytes and lymphocytes exposed to EBV, Concanavalin A, and pokeweed mitogen were assayed, only EBV-exposed lymphocytes expressed EBVCS determinants, which were detectable within 48 hr after infection. Assay of unseparated populations of EBV-exposed primary lymphocytes and immunoglobulin-positive and -negative populations indicated that those cells which express EBVCS determinants are separated as B cells along with those which express the EBV-induced nuclear antigen and that the two antigen-expressing populations are overlapping and may be identical. A polypeptide with an apparent mol wt of 45,000 was precipitated from an EBVCS-positive cell line and was

likely to be the molecule which carries EBVCS determinants. The results indicate that EBVCS determinants are expressed at reduced levels on cell lines established from Burkitt's lymphoma patients relative to expression on other EBV-transformed cell lines. EBVCS determinants are among possible determinants recognized by autochthonous, cytotoxic T cells specific for EBV-transformed cells and may therefore be equivalent to lymphocyte determined membrane antigen (LYDMA); this possibility was supported by the finding that EBVCS and LYDMA were expressed with the same time course in lymphocytes infected with EBV in vitro. If the EBVCS determinants are used by cytotoxic T cells to identify their targets, reduced expression of EBVCS on Burkitt's lymphoma cell lines is consistent with these tumor cells having been selected in vivo to survive that cytotoxic response. (18 Refs)

16. IMMUNOPEROXIDASE TECHNIQUE IN CRYOULTRAMICROTOMY FOR THE DETECTION OF SIMIAN ADE NOVIRUS IN CELL NUCLEI.

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Experimental Medicine, Institut fur Nuclearmedizin/D.K.F.Z., Im Neuenheimer Feld 280, D-69 Heidelberg, W. Germany
Biol Cell; 41(2):153-155 1981

Refinements in the immunoperoxidase technique for labeling of viruses in ultrathin sections of nuclei are described. Simian adenovirus type 7 infected monkey kidney cells were used to localize virus antigens in cell nuclei. Pretreatment of sections with non-immune serum of the same species in which the 'sandwich' (sheep) antibodies were rinsed was effective in prevention of nonspecific adsorptions. Incubation times were also drastically shortened. (13 Refs)

17. MONOCLONAL ANTIBODIES AGAINST ADENOVIRUS TYPE 5: PREPARATION AND PRELIMINARY CHARACTERIZATION.

Russell WC, Patel G, Precious B, Sharp I, Gardner PS
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J Gen Virol; 56(part2):393-408 1981

Eight different hybridoma cell lines producing monoclonal antibodies against the major antigens of human adenovirus Type 5 have been obtained. They were selected by screening initial hybridomas by the fluorescent antibody technique followed by radioimmune precipitation and they reacted with hexon, penton, fiber and 100K polypeptides. Five apparently different epitopes against the hexon antigen were detected showing a spectrum of activity against the hexons of other serotypes, suggesting that the hexon contained a variety of subgroup specificities as well as the previously described group and type specificities. (Author abstract) (26 Refs)

18. STIMULATION OF DNA POLYMERASE ALPHA BY A NUCLEAR DNA/PROTEIN COMPLEX.

Balabanova H, Fridlender BR, Anderer FA
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J Supramol Struct Cell Biochem; 16(1):1-13 1981

A complex containing nuclear DNA, DNA polymerase (DPase), and simian virus 40 (SV40) T-antigen was isolated from nuclei of STU-A/232B transformed murine fibroblasts. Removal of DPase by ultrasonication and chromatographic separation left a DNA/T-antigen complex which stimulated the activity of DPase alpha approx 10-fold. Gel electrophoresis disclosed protein components of the complex with mol wt of 120,000, 94,000, 76,000, 54,000, and 46,000. Separation of DPase activity from T-antigen-specific complement fixation activity resulted in a loss of DPase activity. DPase-stimulation activity (DSA) was adsorbed by protein A-Sepharose loaded with specific IgG from SV40 tumor-bearing mice or antisera against the 94,000 or 76,000 mol wt complex fractions. DSA was partially inhibited by the same antisera. DSA was abolished by pretreatment with either trypsin or deoxyribonuclease I, but was not affected by heating to 80 C for 10 min. (49 Refs)

19. USE OF MONOCLONAL ANTIBODIES AS PROBES OF SIMIAN VIRUS 40 T ANTIGEN ATPASE ACTIV ITY.

Clark R, Lane DP, Tjian R
Dept. Biochemistry, Univ. California, Berkeley, CA, 94720
J Biol Chem; 256(22):11854-11858 1981

We have investigated the ATPase activity of simian virus 40 (SV40) large T antigen by using monoclonal antibodies as specific probes of enzymatic activity. Three hybridoma cell lines secreting anti-T antigen antibodies were derived from mice that were immunized with D2 T antigen, an SV40 T antigen-related protein. Monoclonal antibodies secreted by these hybridomas bind to three distinct T-antigen determinants. In order to bind to T antigen, the three antibodies required amino acid residues coded by the region of the A gene between 0.37 and 0.29 map unit. Two of these antibodies (DL3C3 and DL3C4) strongly inhibited T antigen ATPase activity. The third antibody (DL3C5) only weakly inhibited the ATPase activity possibly by decreasing the affinity of T antigen for ATP. These results demonstrate that the ATPase activity is intrinsic to T antigen and suggest that the ATPase function of T antigen maps on SV40 A gene between 0.37 and 0.29 map unit. A T antigen-specific ATPase assay capable of detecting low levels of T antigen in crude extracts of SV40 infected cells was developed by using 3C5 to immobilize an active form of the enzyme. These results indicate that monoclonal antibodies can be used as probes of enzyme structure and function. (Author abstract) (37 Refs)

20. MURINE TERATOCARCINOMA: A MODEL FOR VIRUS-CELL INTERACTION IN A DIFFERENTIATING CELL SYSTEM.

Friedrich TD, Lehman JM
Jackson Lab., Bar Harbor, ME, 04609
J Supramol Struct Cell Biochem; 15(2):205-211 1981

Infection of murine teratocarcinoma stem cells with simian virus 40 (SV40) was attempted. Cells were cultured from embryonal carcinoma lines 247DESCl2, which originally produced various differentiated cells, and PCC4azal, which can be chemically induced to differentiate. Cell cultures were exposed to SV40. Infection with SV40 was determined by measuring production of T antigen by immunoprecipitation. No infection could be detected in either 247DESCl2 or PCC4azal cells. Attempts to produce infection and consequent appearance of T antigen included multiple infections of different pools of non-plaque-purified SV40, exposure of cell cultures to 100 ug diethylaminoethyl-dextran/ml for 45 min, pretreatment with 4-nitroquinoline-1-oxide for 24 hr, and coinfection with adenovirus. Measurement of 5-bromo-2'-deoxyuridine uptake indicated no detectable synthesis of viral DNA in PCC4azal cells. (24 Refs)

21. THE SV40 72 BASE REPAIR REPEAT HAS A STRIKING EFFECT ON GENE EXPRESSION BOTH IN SV40 AND OTHER CHIMERIC RECOMBINANTS.

Moreau P, Hen R, Wasylyk B, Everett R, Gaub MP, Chambon P
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Nucleic Acids Res; 9(22):6047-6068 1981

By introduction of recombinant plasmids into monkey CV1 cells, we have unambiguously demonstrated that sequences entirely within the 72 bp repeat, which is located upstream of the SV40 early region, are crucial for T-antigen expression in vivo. We have also shown that a DNA fragment containing the 72 bp repeat, inserted directly before chicken conalbumin or adenovirus-2 major late promoter sequences in chimeric plasmids where these promoters replace that of the SV40 early genes, caused a dramatic increase in the expression of T-antigen in vivo. This effect was independent of the orientation of the 72 bp repeat, but was sensitive to its location within the plasmid. When the 72 bp repeat was separated from the promoter sequences, T-antigen expression was reduced. Insertion of the 72 bp repeat into equivalent plasmids containing no known eukaryotic promoter sequences (plasmids which were not detectably expressed in vivo) gave rise to a measurable, but smaller level of expression. The stimulation of expression by the 72 bp repeat is cis-acting: it required covalent linkage to the recombinant. We discuss the possibility that the 72 bp repeat region in SV40 may act as a bi-directional entry site for RNA polymerase B such that promoter sequences linked to the repeat are more efficiently utilized. (Author abstract) (41 Refs)

22. TRANSFORMATION OF RAT FIBROBLASTS BY CLONED DEFECTIVE POLYOMA DNA.

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Arch Int Physiol Biochim; 89(3):225-233 1981

To define the sequence of polyoma (Py) DNA that is essential for cell transformation, defective Py DNA molecules were cloned in plasmid (p) BR322 and the recombinant plasmids were tested for their capacity to transform Fischer rat 3T3 cells in culture. Recombinant plasmids containing an intact proximal portion of the early region were able to transform. All DNA's capable of transforming cells contained an intact 5'-portion of the early region, ie, the region mapping between 70 and 100 map units. pH-df55, the recombinant lacking the DNA sequences extending from 92 to 24 map units, failed to transform. This shows the importance of DNA sequences encoding the C-terminal portion of Py middle T antigen in transformation. The frequency of transformation was of the same order for the three strains of Py virus. Transformation frequency varied little for recombinants containing an intact early region (such as pB4 and pH9) than those carrying only the proximal portion of the early region (such as pPA8). Furthermore, cells transformed by the proximal portion of the early region (PA series) grew as fast as those established by transfection with the complete Py genome (H series). Although the results do not exclude the possibility that small T antigen may play some role in transformation, they indicated that this antigen cannot be responsible for inducing the expression of the transformed phenotype. (28 Refs)

23. USE OF AN AGAR CULTURE TECHNIQUE FOR ESTABLISHING LYMPHOID CELL LINES FROM MAREK'S DISEASE LYMPHOMAS.

Payne LN, Howes K, Rennie M, Bumstead JM, Kidd AW
Houghton Poultry Res. Station, Houghton, Huntingdon, Cambs., PE17 2DA, England

Int J Cancer; 28(6):757-766 1981

Lymphoblastoid cell lines derived from Marek's disease (MD) lymphomas have been established with difficulty by a number of workers. We have compared with conventional liquid culture methods the efficiency of a new technique for establishing lymphoid cell lines in which lymphoma cells were cultured initially in agar medium. Cell from 39/79 lymphomas gave rise to loose lymphoid colonies in the seeded agar after 7 days' incubation at 41 C. Two types of macrophage colony also developed. When lymphoid colonies in agar were transferred to liquid culture, 23/39 gave rise to permanent lymphoid cell lines, compared with 8/33 comparable cultures initiated in liquid medium. Twenty-nine new cell lines have been developed from Rhode Island Red, line 6 and line 7 chickens. All carry T-cell markers and the MD tumor-associated surface antigen (MATSA) and showed variable but low responsiveness to lectin mitogens. The new cell lines, when first established, consisted mainly of small, lymphocytoid cells but, after varying times, these changed into typical lymphoblastoid lines and an increased expression of an embryonic antigen was associated with this change. The lymphocytoid line cells were more slowly growing and density-dependent than were the lymphoblastoid cells, and lymphocytoid lines grew better at 41 C and lymphoblastoid lines better at 37 C. MD virus could be rescued from some of the lines but others appeared to be true nonproducers. (Author abstract) (21 Refs)

24. BIOCHEMICAL TRANSFORMATION OF MOUSE CELLS BY VARICELLA-ZOSTER VIRUS.

Yamanishi K, Matsunaga Y, Ogino T, Lopetegui P
Dept. Virology, Res. Inst. Microbial Diseases, Osaka Univ., Yamadakami, Suita, Osaka 565, Japan

J Gen Virol; 56(part2):421-430 1981

Mouse L cells lacking the enzyme thymidine kinase (Ltk-) were infected with varicella-zoster virus (VZV). Even though virus did not replicate in Ltk- cells, the presence of virus antigen could be observed by use of an anti-complement immunofluorescent technique at 4 hr post-infection and the VZV-specific thymidine kinase could be detected in VZV-infected Ltk- cells. Ltk- cells were converted to a tk+ phenotype (Ltk+) by infection with cell-associated VZV. Clones possessing the ability to grow in selective medium were isolated and cultured successfully for more than 20 passages. One of the clones grew very slowly, but other clones showed almost the same growth rate as that of the parental Ltk- cells. The chromosome analyses of Ltk- cells and transformed cells revealed that the isolated clones were of mouse origin. VZV-specific antigen could be detected in the nuclei of Ltk+ cell clones by an immunofluorescent test, while tk activity was greatly enhanced in extracts prepared from transformed cells and its activity was neutralized by hyperimmune serum against VZV. (Author abstract) (26 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

25. VARIATION OF EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS ON TUMOR CELLS: ABSENCE OF H-2KK-GENE PRODUCTS FROM A GROSS-VIRUS-INDUCED LEUKEMIA IN BALB.K.

Schmidt W, Leben L, Atfield G, Festenstein H
Dept. Virology FB23, Justus Liebig Univ., Frankfurter Str. 107, D-6300 Giessen, W. Germany
Immunogenetics; 14(3/4):323-339 1981

The antigenic profile of the K-GV tumor of BALB.K origin, induced by Gross virus and maintained in vitro and in vivo, was investigated by serological and immunochemical methods and techniques of cell-mediated immunity. The H-2Kk-gene products were absent by several criteria: (1) monoclonal antibody and conventional alloantisera directed against the H-2Kk antigenic specificities were nonreactive by direct testing and by absorptions. (2) H-2Kk products could not be precipitated from glycoprotein or protein extracts of the radiolabeled K-GV tumor. (3) Cytotoxic effectors against H-2Kk produced by sensitization in vitro and in vivo failed to kill K-GV target cells. (4) The tumor could neither stimulate BALB.B congenic mice to produce cytotoxic effectors nor specific cytotoxic antibody against H-2Kk-gene products. In contrast, the H-2Dk antigen was readily detectable by all these criteria. These findings therefore describe a tumor which has selectively lost the H-2K-gene products. The K-GV tumor was able to generate Gross-virus-specific CTL, but had greatly reduced susceptibility to lysis by Gross-virus-specific CTL generated by H-2K expressing AKR (H-2k) tumors. These findings have important implications for the associative recognition of tumor antigens and the immune surveillance of virally induced tumors. (Author abstract) (49 Refs)

26. INDUCTION OF LYMPHOMA IN ANTIGENICALLY STIMULATED ATHYMIC MICE.

Baird SM, Beattie GM, Lannom RA, Lipsick JS, Jensen FC, Kaplan NO
Dept. Pathology, Veterans Admin. Medical Center, San Diego, CA, 92161
Cancer Res; 42(1):198-206 1982

Athymic mice infected with pinworms or carrying human tumor xenografts frequently develop a lymphoproliferative disorder which eventually leads to lymphoma. By immunofluorescent analysis of involved tissues, the lymphomas appear to be mixtures of null cells, B-cells, and T-cells. When each lymphoma is established in tissue culture, a predominant cell type grows out. We have now es tablished lymphoma lines of null cells, B-cells, and T-cells. Lymphoma development is preceded by the secretion into the bloodstream of large amounts of murine leukemia virus mol wt 70,000 glycoprotein antigen; however, very little virus is produced. In vivo, the expression of viral envelope antigen appears within a few days after human tumor transplantation and precedes the development of lymphoma by about a mo. Cells expressing viral antigens are first seen in the diffuse cortex of lymph nodes and the periarteriolar white sheath of the spleen, the tissue domains in which lymphomas also first appear. (Author abstract) (21 Refs)

27. INCREASED EXPRESSION OF IA ANTIGENS ON THYMOCYTES FROM LATE PRELEUKEMIC AND LEUKEMIC ARK MICE.

Zielinski CC, Datta SK, Waksal SD
Cancer Res. Center, 136 Harrison Ave., Boston, MA, 02111
Immunogenetics; 14(1/2):169-176 1981

Thymocyte Ia-antigen levels in AKR mice and 'low leukemia' control mice [C3H, CBA, and (AKR x NZB)F1] were analyzed with the use of fluorescent monoclonal antibodies and a fluorescence-activated cell sorter. The percentage of Ia-expressing thymocytes in AKR mice increased markedly in the late preleukemic and leukemic stages, compared with the percentage in thymocytes from young and early preleukemic mice and the control strains. Nine of 10 late preleukemic and 9/11 leukemic AKR mice showed increased Ia antigen expression that correlated temporally with an increase in thymocyte levels of murine leukemia virus antigens. (30 Refs)

28. NORMAL AND NEOPLASTIC LYMPHOCYTE MATURATION.

Weissman IL, McGrath MS, Pillemer E, Hollander N, Rouse RV, Jerabek L, Stevens SK, Scollay RG, Butcher EF
Lab. Experimental Oncology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
J Supramol Struct Cell Biochem; 15(3):303-314 1981

Maturation of normal and neoplastic lymphocytes is described. Inducer lymphocytes carry the marker Lyt 1 and recognize allogeneic cells or foreign antigens on the basis of the major histocompatibility complex (MHC) I. Cytotoxic T cells carry the markers Lyt 2 and 3 and recognize allogeneic cells or foreign antigens on the basis of K/D markers. Most T lymphocytes are small cells in G0 phase. G0 Lyt 1 cells recognize region I markers and produce T cell growth factor, which maintains proliferation of other T lymphocytes, including at least some Lyt2 and 3 cells. Thymocyte precursors originate from cells in the yolk sac and are produced throughout life in the bone marrow. Lymphoblasts are located mainly in the thymic cortex and produce T lymphocytes, some of which migrate to the thymic medulla or to other organs. In the thymus lymphocyte come in contact with nurse, cortical thymic epithelial, and spatulate epithelial cells, which bear K/D and I MHC markers. Migration and peripheral location of maturing T and B cells is controll ed by surface receptors expressed on the cell surface. Lymphomagenesis may result from binding of retroviruses to lymphocytes bearing specific antigen-specific receptors for retrovirus envelope moieties. Infection of the lymphocytes by the virus would then result in production of viral envelope material, triggering increasing abnormal proliferation of lymphocytes. (50 Refs)

29. INDEPENDENCE OF H-2 AND VIRAL ANTIGENS ON THE CELL SURFACE AND ABSENCE OF H-2 ANTIGENS ON MURINE LEUKEMIA VIRUS AND MOUSE MAMMARY TUMOR VIRUS PARTICLES.

Calafat J, Demant P, Janssen H
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Immunogenetics; 14(3/4):203-220 1981

By indirect immunoelectron microscopy we tested for the presence of H-2 antigens on murine mammary tumor virus (MMTV) and murine leukemia virus (MuLV) particles. The association of H-2 antigens and viral antigens on the virus-infected cell surface was investigated with antibody-induced redistribution. Mammary tumor cells and leukemia cell lines with

different H-2 genotypes and carrying different MuMTV or MuLV were used. No H-2 antigens could be demonstrated on the envelope of MMTV and MuLV particles, even after the permeabilization of their envelopes with saponin. On the surface of virus-infected cells antibody-induced patching or capping of the viral antigens did not result in copatching or cocapping of the H-2 antigens. In the reciprocal tests no co-redistribution of viral antigens with H-2 antigens was seen. Our experiments failed to show any physical association between H-2 antigens and MMTV or MuLV antigens on the cell surface. (Author abstract) (45 Refs)

30. POSSIBLE ROLE OF ENDOGENOUS MMTV VIRUS IN CHEMICAL MAMMARY GLAND CARCINOGENESIS IN MICE.

Komarova EA, Kriukova IN
Lab. Immunology of Oncogenic Viruses, All-Union Cancer Res. Inst., Moscow, USSR
Biull Eksp Biol Med; 91(9):339-342 1981

The effect of immunization with inactivated endogenous MMTV virus on the yield of dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors was studied in BALB/c mice free of exogenous virus. The animals were first administered DMBA (1 mg/day, 1.5 mo, po); then, 1 wk later, they were immunized with formaldehyde-treated suspension of MMTV. Control mice were immunized with Moloney leukemia virus (MuLV). Mammary gland neoplasms were detected in 21% of the mice immunized with MMTV, compared with 39% of MuLV-immunized mice and 40% of nonimmunized mice. The av latent period of tumor development in the MMTV-immunized mice was 119 days, compared with 88 days in the MuLV-immunized mice and 82 days in nonimmunized mice. Indirect immunofluorescence analysis showed expression of gp52 and p27 viral antigens in tumor tissues from both the immunized and the control mice. (11 Refs) (In RUS)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

31. T CELL RECOGNITION OF MOLONEY LEUKEMIA VIRUS PROTEINS: III. T CELL PROLIFERATIVE RESPONSES AGAINST GP70 ARE ASSOCIATED WITH THE PRODUCTION OF A LYMPHOKINE INDUCING 20 ALPHA-HYDROXYSTEROID DEHYDROGENASE IN SPLENIC LYMPHOCYTES.

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Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
J Immunol; 127(6):2565-2570 1981

One of the characteristic cellular immune responses associated with the regression of Moloney leukemia/sarcoma virus-induced tumors is a T cell proliferative response against the major viral envelope glycoprotein, gp70. The results described here demonstrate that associated with this proliferative response is the production of a lymphokine, Interleukin 3 (IL-3). The production of IL-3 was immunologically specific and showed the same specificity as that observed in blastogenic responses. IL-3 production was dependent upon an antigen-specific Thy-1.2+, Lyt-1+, 2-lymphocyte subpopulation but did not require the presence of an Ia+ or an adherent accessory cell. The results also suggested that IL-3 may constitute one of the blastogenic factors previously shown to be involved in the proliferative response to gp70. In particular purified IL-3 w found to induce proliferation of both normal and immu nylon wool purified splenic lymphocytes. The phenotype the responding lymphocyte subpopulation was Thy-1.2-, Lyt , 2-, Ig-, and Ia-. Maximal IL-3 production occurred appro mately 48 hr after the addition of antigen and its producti was significantly blocked by mitomycin C. These character tics were unlike those for the general production of blastogen factor activity suggesting that IL-3 is responsible for only minor component of the proliferative response. (Author a stract) (19 Refs)

32. USE OF HYBRIDOMA-RESISTANT VARIANT CELL LINES TO STUDY H-2DB/FMR-SPECIFIC CYTOTOXIC T CELLS.

Chapdelaine JM, Rajan TV, Nathenson SG, Lilly F
Dept. Genetics, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Immunogenetics; 14(5):429-436 1981

An H-2Db heterozygous tumor cell line and a variant sub clone bearing a mutant gene product were used to analyze th H-2Db specificity of cytotoxic T lymphocytes (CTL) generat ed during a Moloney murine sarcoma virus (MSV) infection When the mutant cells were used as targets for MSV-specific CTL, the amount of cell lysis, compared with that seen with the nonmutant parental cells, was drastically decreased. How ever, cells of the mutant clones remained susceptible to allo geneic CTL specific for the nonmutant H-2Db molecule. The mutant cells also did not differ from the parent cells in their level of viral antigen expression. Biochemically the parental and mutant molecules were similar but not identical. The data indicate that minor alterations of the H-2 antigens caused by somatic mutation may prevent virus-infected cells from being recognized as targets by CTL. (Author abstract) (18 Refs)

33. INHIBITION OF T CELL-MEDIATED FUNCTIONS BY MVM(I), A PARVOVIRUS CLOSELY RELATED TO MINUTE VIRUS OF MICE.

Engers HD, Louis JA, Zubler RH, Hirt B
Dept. Immunology and Virology, Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland
J Immunol; 127(6):2280-2285 1981

A purified preparation of MVM(i), a murine parvovirus closely related to minute virus of mice (MVM), was found to inhibit various functions mediated by murine T cells in vitro. Addition of MVM(i) virus to secondary allogeneic mixed leukocyte cultures resulted in the inhibition of both lymphocyte proliferation (3H-thymidine incorporation) and the generation of cytolytic T lymphocyte activity but not interferon production. MVM(i) virus also inhibited the growth and cytolytic activity of several cloned, long-term Lyt-2+ cytolytic T cell lines. Furthermore, the antigen-induced proliferative responses of parasite- (Leishmania) specific Lyt-1+ T cells in vitro was abrogated by the addition of MVM(i) virus to the culture. Finally, the suppression of an in vitro antibody response to SRBC by MVM(i) virus was the result of the inhibition of T helper cells required for the B cell response. These suppressive effects were specific for MVM(i); parallel studies in which the prototype MVM parvovirus was used showed no significant inhibition in the various systems tested. (Author abstract) (32 Refs)

34. ACCESSORY CELLS IN THE IN VITRO GENERATION OF TYPE C VIRUS-SPECIFIC T KILLER LYMPHOCYTES: II. DEMONSTRATION OF A T HELPER CELL IN THE SPLEEN OF IN VIVO PRIMED MICE.

Gomard E, Wybier-Franqui J, Simmler MC, McKenzie IF, Levy JP
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J Immunol; 127(6):2291-2295 1981

The existence of a helper T cell cooperating with cytolytic T lymphocytes (CTL) in cell-mediated anti-tumor responses specific for the virus-induced FMR antigens can be demonstrated by using unprimed thymocytes as CTL precursors and in vivo primed irradiated spleen cells as helper. The helper T cells express Thy-1.2 and Lyt-1.2 antigens at their surface, but not Lyt-2.2. The helper function required the presence of macrophages to be detected, is antigen specific, and appears unusually radiosensitive compared with previously described helper T cell function. (Author abstract) (27 Refs)

35. MINOR HISTOCOMPATIBILITY ANTIGENS DO NOT ENHANCE BALB/C ANTI-SV40 TASA RESPONSE.

Nanni P, De Giovanni C, Galli MC, Grilli S, Lollini PL, Nicoletti G, Prodi G
Istituto di Cancerologia, Via S. Giacomo 14, I-40126 Bologna, Italy
Br J Cancer; 44(4):588-591 1981

Possible enhancement of the immune response to simian virus-40 (SV40)-induced tumor-associated surface antigens (TASA) was studied in major histocompatibility complex (MHC)-matched mice after immunization with TASA along with minor histocompatibility antigens (as adjuvant antigens). An in vitro cytotoxicity test using BALB/c mouse spleen cells immunized with cell lines differing at multiple minor histocompatibility loci (either the syngeneic cell line KB/cSV or the KD2SV cell line) did not detect an adjuvant effect of the minor histocompatibility antigens. In the Winn neutralization assay, 9-10 wk-old female mice were immunized sc with 10(6) KD2SV, KB/cSV, or mKSA-Tu5 cells. Twenty days later, spleen cells from 2-3 animals were pooled, mixed with 10(5) freshly harvested mKSA(ASC) cells at different ratios (25:1, 50:1, 100:1), suspended in 0.2 ml phosphate buffered saline, and injected sc into the left hind legs of 11-12 wk-old BALB/c females. Survival of tumor-free animals failed to indicate an adjuvant effect by minor histocompatibility antigens. Both tests failed to detect enhancement of the immune response against SV40-transformed syngeneic cells in BALB/c mice who are immunized with H-2 matched SV40-transformed cells differing at multiple minor histocompatibility loci. (16 Refs)

36. PREPARATION OF STABLE TARGET CELLS FOR ANTI-HERPES SIMPLEX VIRUS CYTOTOXIC T LYMPHOCYTES.

Sonoda S, Hitsumoto Y, Utsumi S, Takami S, Oseto M, Minamishima Y
Ehime Prefectural Inst. Public Health, Sanban-cho, Matsuyama, Ehime 790, Japan
Microbiol Immunol; 25(10):999-1010 1981

With the use of SKa, an avirulent strain of herpes simplex virus (HSV), and a methylcholanthrene-induced mouse sarcoma cell line (Meth A cells), a reliable target cell system was developed for detection of cell-mediated cytotoxicity directed against HSV-infected cells. Also discussed are the assessment of improved measurement for HSV-specific cytotoxic T lymphocytes (CTL) generated in BALB/c mice, and the practical value of avirulent HSV for the study of cell-mediated immunity against HSV. SKa propagated in Vero cells did not replicate in Meth A cells when infected at multiplicity of infection (moi) 3, whereas strain KOS at the same moi replicated in these cells as well as in Vero cells. Generation of HSV-antigen by SKa advanced so slowly that it reached the max level at 18 hr post-infection (pi) while KOS infection resulted in a rapid production of HSV antigens which was accomplished within 6 hr pi and followed by abrupt response of cytolysis. SKa-infected Meth A cells released no more 51Cr than noninfected control cells, whereas KOS-infected cells induced an abrupt increase in 51Cr-release at around 8 hr pi. SKa-infected Meth A targets were specifically lysed by immune spleen cells stimulated with HSV-infected Meth A antigens, but n ot by spleen cells treated with noninfected Meth A cells alone. Thy-1 antigen positive cells are responsible for HSV-specific cytotoxicity. The system described should be valuable in studies of cell-mediated cytotoxicity directed against HSV-infected cells. (42 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

37. THE IMMUNOTHERAPEUTIC EFFECT OF A POLYANTIGENIC VACCINE IN ANIMAL TUMOR MODELS.

Colon JI, Marchand AM, Roman Franco AA, Santiago Delpin EA
Puerto Rico Cancer Center, Puerto Rico
Bol Asoc Med P R; 73(4):162-167 1981

A polyantigenic vaccine (PAV) was tested against mouse Ehrlich ascites tumor (EAT), adenocarcinoma (AC), and chondrosarcoma (CS) in BALB/c and C3H/HeJ mice. Tumor inoculations consisted of 10(5) cells injected sc. PAV consisted of influenza virus and bacterial vaccines suspended in peanut oil and Arlacel A. Doses of 0.1 ml PAV were given weekly, beginning 1 wk after tumor inoculation. Tumors developed in 37.5% of PAV-treated AC-bearing mice compared with 87.5% of untreated controls. Mortality rate was 71% among controls and 0% among PAV-treated mice. PAV-treated EAT-bearing mice showed a 44% mortality rate compared with 89% for untreated controls. EAT growth resumed if PAV treatment was stopped. BCG treatment protected 10% of CS-bearing mice, while PAV protected 50%. Together PAV and BCG protected 58% of CS-bearing mice. All untreated controls died. The viral component of PAV was more active than the bacterial component, but not as effective as complete PAV. Results indicate the effectiveness of PAV against some experimental tumors. (5 Refs)

OTHER RELATED STUDIES

38. ON THE MOLECULAR BASIS OF ONCOGENESIS.

Ahlgren JD
Div. Medical Oncology, Vincent T. Lombardi Cancer Res. Center, Georgetown Univ. Sch. Medicine, Washington, DC, 20007
J Theor Biol; 93(1):217-223 1981

A molecular basis for the development of neoplasia is proposed based on viral disruption of genomic regions coding for proteins which control entry into the cell cycle from Go. Such

disruption could also be effected by chemically or radiation-induced mutation. Under such conditions normal control proteins would no longer be synthesized. As the available intracellular pool of normal protein is used up, more and more cells would remain in the proliferative cycle. Fetal genes might also be derepressed, with a concomitant reduction in the expression of adult genes, resulting in a shift in transformed cells toward a less differentiated state. The expression of derepressed fetal genes would account for observed fetal antigens on tumor cells. The somatic cell destined to form a tumor clone may have multiple abnormal intracellular proteins due to the random nature of simultaneous point mutations in the genome. Endogenous transposable elements may also cleave control cistrons. (35 Refs)

39. BIOLOGICAL AND IMMUNOLOGICAL MARKERS IN ACUTE LEUKAEMIA.

Lopez Borrasca A, Gonzalez M, Hernandez F, Ledesma M, Corrales A, San Miguel J
Servicio de Hematologia, Hospital Clinico Universitario, Salamanca, Spain
Sangre (Barc); 26(5B):756-782 1981

The authors present a review of the value of immunologic and enzymatic markers in the diagnosis of the different types of acute leukemia (AL). The addition of such markers to the classical morphologic and cytochemical criteria is advisable since they provide the means for AL subclassifications to be used with therapeutical purposes. The markers are divided into (a) surface receptors: sIg, C receptors, Fc receptors, non-immunologic spontaneous rosettes with different red-cells and viral receptors; and (b) surface antigens, including T-lymphocytes surface antigen, B-lymphocyte antigens, common ALL antigen and myeloid cells antigen. Their significance is detailed, along with other data including their study techniques, the levels in different leukemic populations, and the value of such markers in the immunologic differential-diagnosis of the leukemias. The enzymatic markers, terminal deoxynucleotidyl transferase, adenosine-deaminase, nucleoside-phosphorylase, 5'-nucleotidase, and hexosaminidase (N-acetyl-B-glucosaminidase) are considered. Following the pattern referred to, an analysis is made of the significance of, and study methods for, these sort of markers, along with their clinical interest and the correlation they may show with the immunologic markers mentioned above. Classifications are suggested based on the phenotypes of the leukemic cells. These phenotypes correspond to T-cell, B-cell, and non-T, non-B lymphoblastic leukemias, as well as to the blastic crises of chronic granulocytic leukemia; and the phenotypes of the acute myeloblastic leukemias are also considered. The application of the methodology commented in this paper has provided a new variant, the pre-B acute leukemia, which is characterized by possessing cIgM. (173 Refs) (In SPA)

40. ANTI-K562 CELL MONOCLONAL ANTIBODIES RECOGNIZE HEMATOPOIETIC PROGENITORS.

Young NS, Hwang-Chen SP
Clinical Hematology Branch, Natl. Heart, Lung, and Blood Inst., NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(11,part2):7073-7077 1981

The K562 leukemia cell has properties of self-renewal and pluripotency similar to those of the hematopoietic stem cell. Monoclonal antibodies to K562 cells have been produced by using hybridoma technology. By radioinmunoassay, some anti-K562 cell antibodies also bind to RBC antigens or peripheral blood mononuclear cells; others are more specific for K562 cells. Antibody binding to hematopoietic progenitors was assayed by using the ability of these cells to form colonies in vitro. After exposure of hu man bone marrow cells to anti-K562 antibodies and complement, myeloid or erythroid colony formation was inhibited. Some of the inhibitory antibodies showed little binding to mature blood cells by radioimmunoassay, immunofluorescence, and complement cytotoxicity, suggesting that they recognize antigens specific to undifferentiated cells. With the fluorescence-activated cell sorter, one inhibitory antibody was shown to stain only 3% of bone marrow cells. Inhibitory anti-K562 antibodies also bind to myelogenous leukemia cells and virus-transformed lymphocytes. Thus, these antibodies appear to recognize antigens shared by normal hematopoietic progenitors, leukemic cells, and transformed lymphocytes. (Author abstract) (26 Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. TYPE C VIRUS PARTICLES IN A CORD T-CELL LINE DERIVED BY CO-CULTIVATING NORMAL CORD LEUKOCYTES AND HUMAN LEUKAEMIC T CELLS.

Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, Nagata K, Hinuma Y
Dept. Medicine, Kochi Medical Sch., Kochi 781-51, Japan
Nature; 294(5843):770-771 1981

Cocultivation of adult T-cell leukemia (ATL) cells with cord WBC from a male infant was used to establish a T-cell line that expresses ATL-associated antigens (ATLAs) and contains numerous C-type virus particles. The ATLAs were detected

HE 20.3173/2:

by indirect immunofluorescence using ATL patients' sera and fluorescein isothiocyanate-conjugated goat antihuman IgG. Thin-section electron microscopy revealed the virus particles, which are predominantly mature and consist of an electron-dense nucleoid and an outer membrane. (8 Refs)

2. TRANSFORMATION OF NORMAL HUMAN CORD LYMPHOCYTES BY CO-CULTIVATION WITH A LETHALLY IRRADIATED HUMAN T-CELL LINE CARRYING TYPE C VIRUS PARTICLES.

Miyoshi I, Yoshimoto S, Taguchi H, Ohtsuki Y, Kubonishi I, Shiraishi Y, Akagi T

Dept. Anatomy, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan

Gan; 72(6):997-998 1981

Normal human cord WBC were co-cultured with lethally irradiated MT-2 cells to produce a T-cell line of cord WBC origin which harbored type C virus particles and adult T-cell leukemia-associated antigens (ATLA). On the 11th day of culture, 1 x 10(6) lethally x-irradiated (6,000 R) MT-2 cells were added to two of four dishes of cord WBC. Control cultures included two dishes of irradiated MT-2 cells without cord WBC and two dishes of cord WBC alone. All cultures were incubated at 37 C in a humidified 7.5% CO2 atmosphere. Two wk after co-culture, scattered foci of cell aggregates were observed on the sheets of macrophages. Continuous growth of cells developed in two of the co-cultured dishes, and this cell line, designated Ok, was maintained in culture for 3 mo. The Ok line consisted of mostly immature lymphoid cells with multinucleate giant cells. Sixty-six percent of the Ok cells formed spontaneous rosettes with neuraminidase-treated sheep RBC. Most of the Ok cells were positive for Leu-1 and OK11, but negative for Leu-2a and Leu-3a. None of the 145 Ok cells studied contained a Y chromosome; 41/46 cells had a 46,XX karyotype. Electron microscopy revealed many type C virus particles in the extracellular spaces. Most of the Ok cells were positive for ATLA when reacted with ATL patient's sera. The cultured cells gave a positive reaction with five sera from ATL patients but not with five sera from normal control individuals. These findings suggest that the type C virus was apparently transmitted from the MT-2 cells to the cord lymphocytes during co-cultivation. (8 Refs)

3. DETECTION BY RADIOIMMUNOASSAY OF ANTIGENS RELATED TO THE P30 POLYPEPTIDES OF PRIMATE TYPE C ONCOVIRUSES IN PERIPHERAL LEUKOCYTES FROM PATIENTS WITH CHRONIC MYELOGENOUS LEUKAEMIA.

Toth FD, Vaczi L, Kiss J, Rethy A, Kiss A, Rak K

Inst. Microbiology, Univ. Medical Sch., 4012 Debrecen, Hungary

Acta Virol (Praha); 25(6):376-380 1981

Leukocytes from patients with chronic myelogenous leukemia were examined for antigens related to the p30 polypeptides of baboon endogenous virus (BaEV) and gibbon ape leukemia virus (GaLV). Samples from patients with the quiescent phase of the disease proved to be negative or contained p30 of BaEV as the only viral antigen. In cases of blastoid crisis or acceleration, an antigen related to p30 of GaLV could be detected. In five of six patients, acceleration or blastoid crisis was preceded by expression of GaLV p30. (Author abstract) (15 Refs)

4. A CONTROLLED STUDY OF HEPATITIS CORE ANTIBODY (HBCAB) IN PRIMARY HEPATOCELLULAR CARCINOMA AND LIVER CIRRHOSIS IN KENYA.

Bowry TR, Shah MV, Ahmad Z

Immunology Section, Dept. Human Pathology, Univ. Nairobi, Nairobi, Kenya

East Afr Med J; 58(8):576-582 1981

Incidence of hepatitis B virus (HBV) markers was studied in 75 Kenyan patients with confirmed liver disease. Among these patients, 15 had liver cirrhosis (LC), 13 had LC and concomitant primary hepatocellular carcinoma (PHC), and 47 had PHC. Presence of hepatitis B surface antigen (HBsAg) was detected in 40% of the patients with LC, in 47% of the patients with LC + PHC, and in 46% of the patients with PHC. Among the HBsAg-positive patients, high titers of hepatitis B core antibody (HBcAb) were detected in 100% of the patients with LC, 100% of those with LC + PHC, and 90% of those with PHC. HBcAb as a sole marker of HBV was detected in 13% of the patients with LC, 31% of those with LC + PHC, and 9% of those with PHC. (16 Refs)

5. IN VIVO LOCALIZATION OF TUMOR ASSOCIATED ANTIGENS WITH RADIOACTIVELY LABELED MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Henkel RD, Dressman GR

Baylor College of Medicine, Houston, TX, 77030

Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies were prepared against hepatitis B surface antigen (HBsAg). These preparations were shown to react with HBsAg secreted by human hepatoma cells from the cell line designated PLC/PRF/5. These cells and cells from another human tumor cell line (Hep-2) which is HBsAg negative, were inoculated sc into BALB/c background nude mice. The anti-HBsAg monoclonal antibodies and nonspecific monoclonal antibodies of the same isotype were purified by salt precipitation and gel filtration and labeled with 131I-using the Hunter-Greenwood method. Three wk after cell inoculation, the nude mice were injected with either the anti-HBsAg antibodies or with the non-specific antibodies. Eight days later the mice were sacrificed and each major organ and tumor were weighed and counted to determine the amount of radioactivity per g of tissue. The results indicated that: 1) more radioactivity was found in the tumors bearing the HBsAg than the Hep-2 tumor when anti-HBsAg antibodies were used and; 2) no such difference could be seen when the nonspecific antibodies were used. (no Refs)

6. THE HEPATITIS-B VIRUS AND HEPATOCELLULAR CARCINOMA.

Kew MC

Dept. Medicine, Witwatersrand Univ. Medical Sch., Johannesburg, South Africa

Semin Liver Dis; 1(1):59-67 1981

The association between hepatocellular carcinoma (HCC) and chronic hepatitis-B virus (HBV) is discussed, and various explanations for its etiology are considered. The world-wide geographic distributions of the HBV carrier state and HCC are remarkably similar, with some exceptions. Countries in sub-Saharan Africa and the Far East, eg, with HBV surface antigen carrier rates of 6-14% also have the highest rates of HCC. However, in Greenland, where 7-25% of the population has chronic HBV surface antigen, HCC is nevertheless rare. This

discrepancy could be explained by the absence of a cocarcinogen in the Greenland environment. The most persuasive evidence that an association exists between HCC and HBV is the frequency with which markers of the virus are present in the serum and tissues of patients with this tumor. Alternative explanations to a cause and effect relationship between HBV infection and HCC are discussed. However, no such considered explanations account for the association as well as the postulate that HBV plays a causal role in HCC. (84 Refs)

7. PRIMARY HEPATOCELLULAR CARCINOMA -- ETIOLOGY, PATHOGENESIS, AND PREVENTION.

London WT

Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111

Hum Pathol; 12(12):1085-1097 1981

Worldwide, primary hepatocellular carcinoma may be the most common cancer in men. Usually it occurs in association with cirrhosis or chronic hepatitis. In this article I present evidence that the majority of these cases are associated with, and probably caused by, persistent infection with hepatitis B virus. I also propose a model that describes the role of the hepatitis B virus in the pathogenesis of primary hepatocellular carcinoma. If persistent infection with hepatitis B virus is required for the development of most cases of primary hepatocellular carcinoma, prevention of such infections should prevent most cases of primary hepatocellular carcinoma. A vaccine against hepatitis B virus, prepared from surface antigen particles (HBsAg) harvested from the blood of hepatitis B virus carriers, has been safe and effective in preventing acute infection with hepatitis B virus in adult homosexual men. If it is equally safe and effective in young children, it will be administered widely to populations living in areas endemic for hepatitis B virus infections. Thereafter it may be possible to learn within 5 to 10 years whether the vaccine prevents chronic liver disease. If it does, it will be reasonable to conclude that it will also prevent primary hepatocellular carcinoma. (Author abstract) (47 Refs)

8. DETECTION OF EPSTEIN-BARR VIRAL DNA INTERNAL REPEATS IN THE NASOPHARYNGEAL MUCOSA OF CHINESE WITH IGA/EBV-SPECIFIC ANTIBODIES.

Desgranges C, Bornkamm GW, Zeng Y, Wang PC, Zhu JS, Shang M, De-The G

CNRS Lab., Faculty Medicine Alexis Carrel, 69372 Lyon Cedex 2,, France

Int J Cancer; 29(1):87-91 1982

Fifty-six South Chinese individuals exhibiting IgA antibodies to EBV for 18 mo and presenting nasopharyngeal abnormalities were biopsied. Four nasopharyngeal carcinomas, two at a very early stage, were detected. In 14 other individuals, without clinical or histopathological evidence of tumor, EBV/DNA internal repeats and/or EBNA were detected in the biopsied mucosae. The presence of IgA/EBV antibodies and/or EBV markers in the nasopharyngeal mucosa may characterize pre-cancerous conditions. (Author abstract) (25 Refs)

9. BIOCHEMICAL AND IMMUNOLOGICAL CHARACTERIZATION OF CELLULAR DNA POLYMERASES ALPHA, BETA AND GAMMA, AND A REVERSE TRANSCRIPTASE FROM HUMAN MELANOMA TISSUE.

Chandra P, Balikcioglu S, Mildner B

Zentrum der Biologischen Chemie, Theodor-Stern-Kai 7, D-6 Frankfurt a. Main 70, W. Germany

Cell Mol Biol; 27(2/3):239-251 1981

The present study describes separation and purification of a reverse transcriptase and cellular DNA polymerases from human primary melanoma tissue. The specific requirements with respect to bivalent cations and template-primers for DNA polymerase alpha, DNA polymerase beta and DNA polymerase gamma, as well as for the reverse transcriptase, are reported. Sodium dodecylsulfate gel electrophoresis of the purified enzymes gave estimated values of mol wt of 160,000, 38,000, 100,000 and 68,000 daltons for DNA polymerase alpha, DNA polymerase beta, DNA polymerase gamma and reverse transcriptase respectively. Serological studies have shown that the reverse transcriptase of human melanoma tissue is not antigenically related to cellular DNA polymerase alpha, beta, or gamma, but is antigenically related to reverse transcriptases from baboon endogenous virus (BEV) and RD-114. This is the first human reverse transcriptase showing cross-reactivity to DNA polymerases from endogenous retroviruses. (Author abstract) (24 Refs)

10. HUMAN PAPILLOMAVIRUS (HPV) IN CONDYLOMATOUS LESIONS OF CERVIX: A COMPARATIVE ULTRASTRUCTURAL AND IMMUNOHISTOCHEMICAL STUDY.

Ferenczy A, Braun L, Shah KV

Dept. Pathology, Jewish General Hosp., 3755 Chemin de la Cote Ste. Catherine, Montreal, Quebec H3T 1E2, Canada

Am J Surg Pathol; 5(7):661-670 1981

Cervical condylomata classified histologically as flat, papillary, or endophytic were obtained from 97 patients (16-35 yr old). Transmission electron microscopy (TEM) was used to detect the presence of human papillomavirus (HPV) particles; the immunoperoxidase technique (IPT) was used to detect viral antigen. HPV particles were found in 24/97 specimens by TEM. Viral particles were demonstrated in 21/68 flat and 3/26 papillary condylomata. Viral antigen was found in 47/97 specimens by IPT. All specimens positive by TEM were also positive by IPT, confirming the specificity of the immunological staining. The viral antigen was detected in 38/68 specimens of flat condylomata, in 9/26 papillary condylomata, and in 0/3 endophytic condylomata. Prevalence of HPV correlated with the extent of koilocytosis rather than with histiotype. IPT is of value for further characterizing cervical condylomata and the relationship between HPV infection and cervical intraepithelial neoplasia. (23 Refs)

11. DIAGNOSIS OF PRIMARY BREAST CARCINOMA THROUGH IMMUNOHISTOCHEMICAL DETECTION OF ANTIGEN RELATED TO MOUSE MAMMARY TUMOR VIRUS IN METASTATIC LESIONS: A REPORT OF TWO CASES.

Mesa-Tejada R, Oster MW, Fenoglio CM, Magidson J, Spiegelman S
Inst. Cancer Res., 701 West 168th St., New York, NY, 10032
Cancer; 49(2):261-268 1982

Recent investigations have established that approximately half of human breast carcinomas contain an immunohistochemically detectable antigen which is cross-reactive with the 52,000-dalton major glycoprotein (gp52) of the mouse mammary tumor virus (MMTV). This antigen can be localized in paraffin-embedded sections of routinely fixed tissues using heterologous antibodies to gp52 of MMTV. This report describes two patients with metastatic carcinoma in axillary lymph nodes without any clinical evidence of a primary lesion in the breast or elsewhere. The localization of the gp52-related antigen in paraffin-embedded sections of both metastatic lesions suggested the presence of primary mammary carcinoma. In both instances, this suggestion was ultimately confirmed by the finding of primary lesions in which the gp52-related antigen was also found. (Author abstract) (30 Refs)

12. ROLE OF ONCOGENES IN THE DEVELOPMENT OF TUMORS.

Klein G
Institutionen for tumorbiologi, Karolinska institutet, Stockholm, Sweden
Lakartidningen; 78(41):3575-3577 1981

Recent studies in viral oncogenes are reviewed. The coupling of some normal genes is a common feature of all tumor transformation processes caused by not directly-transforming RNA tumor viruses. Unlike the RNA viruses, the DNA viruses belong to several greatly different groups. Production of the so-called T antigen is a common feature of all DNA tumor viruses. This antigen occurs in all transformed cells. There are at least three virus types (papilloma virus, Epstein-Barr virus (EBV), and hepatitis B virus) contribute to the development of certain human tumors, but their contributions are less direct than in the case of infectious diseases. Only papilloma virus induces tumors directly, and most of them are benign, but papilloma virus may play a certain role in the genesis of some malignant epithelial tumors as well. Hepatitis B virus first causes liver cirrhosis, a precancerous state, the development of the tumor clone being the result of abnormal regeneration. (7 Refs) (In SWE)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

13. EXPRESSION OF EPSTEIN-BARR VIRAL EARLY ANTIGEN IN MONOLAYER TISSUE CULTURES AFTER TRANSFECTION WITH VIRAL DNA AND DNA FRAGMENTS.

Grogan E, Miller G, Henle W, Rabson M, Shedd D, Niederman JC
Dept. Pediatrics, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Virol; 40(3):861-869 1981

Antigens associated with the Epstein-Barr virus (EBV) replicative cycle were found in the nucleus and cytoplasm of human placental, Vero, BSC-1, and owl monkey kidney cells transfected with EBV DNA prepared from several different strains of virus. The number of antigen-positive nuclei increased when transfection was followed by cell fusion induced by inactivated Sendai virus. About 1,200 antigen-positive foci were induced per ug of EBV DNA. On the basis of their reactivity with various well-characterized human sera, it appears that the antigens are part of the early antigen complex. None of the four restrictive endonucleases, EcoRI, HindIII, SalI, and BamHI, destroyed the ability of EBV DNA to induce early antigen. However, only SalI seemed to leave intact the full spectrum of antigen expression by the HR-1 and FF41 strains of EBV DNA. By means of transfection with recombinant DNA plasmids containing different EBV (FF41) DNA fragments generated by EcoRI, we showed that the coding region for early antigen was at least partially contained on the 17.2-megadalton EcoRI B fragment. (Author abstract) (22 Refs)

14. PRESENCE OF EPSTEIN-BARR VIRUS DNA IN TONSILLAR TISSUES.

Brichacek B, Suchankova A, Hirsch I, Sibl O, Rezacova D, Zavadova H, Vonka V
Dept. Experimental Virology, Inst. Sera and Vaccines, 101 03 Prague, Czechoslovakia
Acta Virol (Praha); 25(6):361-370 1981

Sera from 48 tonsillar carcinoma (TC) patients, 48 matched controls and 16 recurrent exudative tonsillitis (RET) patients were examined for the presence of Epstein-Barr virus (EBV) associated nuclear antigen (EBNA), early antigen (EA) and virus capsid antigen (VCA). Higher prevalence and significantly higher antibody titers against all three EBV-associated antigens were observed in TC patients in comparison with controls and RET patients. Patients suffering from anaplastic TC had higher titers of antibodies against VCA and EA than TC patients with other histological diagnoses. Five out of 11 TC biopsies obtained from nine patients were positive for EBV DNA at levels of 0.17, 4 to 5, 15 to 18 and in two cases 3 EBV genome equivalents per cellular genome. Among 16 RET patients, 4 were found positive at levels not exceeding 2.17 EBV genome equivalents per cellular genome. Higher titers of antibody against all EBV antigens were found in TC and RET patients with EBV DNA-positive tonsillar tissue than in those with EBV DNA negative tonsillar tissue. (Author abstract) (34 Refs)

15. THE EVOLUTION OF POLYOMA-TRANSFORMED RAT CELL LINES DURING PROPAGATION IN VITRO.

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Virology; 116(1):207-220 1982

We have previously shown that the presence of a functional viral large T antigen in polyoma-transformed rat cells results in instability of the integrated viral DNA, as manifest by free viral DNA production, excision, and amplification of the integrated viral molecules. It has also been observed that polyoma tumors or transformed cell lines often do not produce functional large T antigen. To determine if an evolution toward the loss of large T-Ag function took place in vitro in polyoma-transformed cell lines, we studied the changes occurring in the integrated viral DNA sequences of a ts-a Py-transformed rat cell line, ts-a H3, upon propagation under conditions permissive (33 C) or nonpermissive (39 C) for large T function. H3 contains a single insertion of a partial tandem of approx 1.2 viral genomes, and at 33 C produces free viral DNA and also

undergoes a high frequency of excision and amplification, involving recombination between homologous portions of viral DNA. While the integrated arrangement of viral DNA sequences remains unchanged at 39 C, in two independent experiments long-term propagation of H3 at 33 C resulted in the emergence of a fully transformed cell population which no longer produced free viral DNA and whose integrated viral DNA pattern was modified. In one of these populations, H3, interruption of the integrated viral coding sequences unique to large T antigen by a segment of host DNA resulted in the loss of large T antigen function. In another population, H3A*-3, the integrated viral DNA had undergone some rearrangement which, however, did not apparently affect large T Ag coding sequences. Since the latter cell population did not produce free viral DNA and was unable to 'rescue' integrated viral DNA sequences from A t-Ag-negative Py-transformed cell line after cell fusion, the large antigen produced by H3A*-3 is probably nonfunctional. These results are consistent with the hypothesis that the presence of large T antigen leads to instability of the viral DNA integration and that this instability is responsible for the selection of large T antigen-negative cells from Py-transformed populations. Possible mechanisms underlying this type of evolution are presented. (Author abstract) (33 Refs)

16. ESTABLISHMENT OF B-LYMPHOBLASTOID CELL LINES FROM MAREK'S DISEASE VIRUS-INDUCED TUMORS IN TURKEYS.

Nazerian K, Elmubarak A, Sharma JM
Regional Poultry Res. Lab., U. S. Dept. Agriculture, 3606 East Mount Hope Road, East Lansing, MI, 48823
Int J Cancer; 29(1):63-68 1982

Four lymphoblastoid cell lines were established from tumors of turkeys inoculated with high doses of the GA strain of Marek's disease virus (MDV). Unlike other MD lymphoblastoid cell lines of chicken origin, these MDV transformed turkey lines appear to be B lymphocytes and produce immunoglobulin. Growth characteristics of these cell lines are slightly different; however, they all produce low levels of MDV-specific antigen and carry the complete genome of the virus as determined by virus rescue in the chicken or in duck embryo fibroblast cultures. These cell lines are pathogenic for chickens and produce virus-induced MD lesions. All four lines are free of the herpesvirus of turkeys, reticuloendotheliosis virus, and three lines are also free of avian leukosis virus. They all have typical normal turkey chromosomes and are positive for Marek's disease tumor-associated surface antigen. (Author abstract) (24 Refs)

17. INDUCTION OF LYMPHOMAS AND TUMOR ANTIGEN BY MAREK'S DISEASE VIRUS IN TURKEYS.

Elmubarak AK, Sharma JM, Witter RL, Nazerian K, Sanger VL
U. S. Dept. Agriculture, SEA-AR, Regional Poultry Res. Lab., 3606 E. Mount Hope Road, East Lansing, MI, 48823
Avian Dis; 25(4):911-926 1981

Mycoplasma-free turkeys were inoculated with the highly pathogenic GA isolate of Marek's disease (MD) virus (MDV), and were observed for lympholytic and lymphoproliferative lesions and humoral and cellular immunocompetence. Inoculated turkey poults became persistently viremic with MDV, with levels of circulating MDV that were lower than in similarly inoculated specific-pathogen-free chickens. The early lytic phase of MD with lymphoid cell destruction and appearance of viral antigen in lymphoid organs was less pronounced than in chickens. Gross lesions in turkey poults after MDV infection were most frequent in spleen and liver but also involved kidneys, gonad, heart, thymus, and peripheral nerves. MD tumors contained cells that reacted with antiserum prepared against chicken MD-tumor-associated surface antigen. This result indicated that MDV induced cellular transformation in turkeys and that the tumor-associated antigen in chickens and turkeys cross-reacted. Several in vitro-propagating B-cell lines were developed from turkey lymphomas. MD in turkeys resulted in immunodepression as it did in chickens. Circulating lymphocytes from turkeys that eventually died of MD or had developed gross tumors were deficient in response to Concanavalin A. (19 Refs)

18. IDENTIFICATION OF A NEW ANTIGENIC VARIANT OF SIMIAN ADENOVIRUS (SV30N).

Zolotarskaia EE, Dreizin RS, Fedorinov VV, Khil'ko SN, Manykin AA, Naroditskii BS, Gurov AV
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Vopr Virusol; (5):581-586 1981

Results of serotyping of a new variant of simian adenovirus SV38 are reported. The antigenic characteristics of the new variant were similar to those of SV30 and SA7. The variant, identified as SV30N, did not induce tumors in hamsters. (8 Refs) (In RUS)

19. PRODUCTION AND CHARACTERIZATION OF MONOCLONAL ANTIBODIES AGAINST THE EPSTEIN-BARR VIRUS MEMBRANE ANTIGEN.

Strnad BC, Schuster T, Klein R, Hopkins RF, Witmer T, Neubauer RH, Rabin H
Frederick Cancer Res. Center, Frederick, MD, 21701
J Virol; 41(1):258-264 1982

Five murine hybridoma lines that produce monoclonal antibodies against Epstein-Barr virus membrane antigen (MA) were established. Immunoprecipitation experiments demonstrated that three of the antibodies precipitated both the 236,000 (236K) MA and the 212K MA. The other two antibodies precipitated the 86K MA. Antibodies against the 236K-212K MA and the 86K MA mediated complement-dependent cytolysis of Epstein-Barr-virus-infected cells. The antibodies against the 86K MA neutralized both the B95-8 and P3HR-1 viruses. (Author abstract) (18 Refs)

20. INTERACTION OF SV40 T-ANTIGEN WITH CHROMATIN IN TUMOR CELLS.

Rheszowska-Wolny I, Sadzinska L, Grobner S, Shliankevich MA, Drize OB, Demina EB, Polotskaia AV
Inst. Oncology, Gliwice, Poland
Biokhimiia; 46(10):1880-1886 1981

Sedimentation analysis and electrophoresis in the polyacrylamide gel showed the presence of T-antigen of simian virus SV40 in the chromatin isolated from SV40-induced Syrian hamster tumors. T-antigen was bound to oligonucleosomes fraction. It was suggested that T-antigen interacts not only with DNA but also with H1 histone. (24 Refs) (In RUS)

21. MUTANT CARRYING DELETIONS IN THE TWO SIMIAN VIRUS 40 EARLY GENES.

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J Virol; 40(3):625-634 1981

We isolated a simian virus 40 mutant, dl2194, which carried deletions in both early genes. One deletion removed 234 base pairs in the 54/59 region within the small-t-antigen coding sequence and the large-T-antigen gene intron. The second deletion removed 57 base pairs at the C terminus of the large-T-antigen coding sequence (0.20 map unit). dl2194 was a viable mutant; it carried a normal helper function for adenovirus growth on monkey cells, and it displayed the transformation properties of a small-t-antigen-negative single mutant. Therefore, none of the known large-T-antigen functions seemed to be altered by the C-terminal deletion. (Author abstract) (34 Refs)

22. T ANTIGEN REPRESSION OF SV40 EARLY TRANSCRIPTION FROM TWO PROMOTERS.

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Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 27(3):603-612 1981

The SV40 early mRNAs encode large (T) and small (t) tumor antigens. During the lytic cycle, the 5' termini of the early mRNAs undergo a shift: shortly after infection only an initiation site downstream from the TATA box is utilized; later an upstream initiation site becomes prominent. Both initiation sites are utilized in an in vitro transcription extract. D2T, a T antigen analog, specifically represses transcription in vitro from both initiation sites, but at different concentrations. Binding of D2T to Site I supp resses initiation from the site downstream of the TATA box; binding to Sites II and I suppresses initiation from the upstream site. The role of T antigen binding in repression of transcription and in the shift of initiation sites on the early strand is discussed. (Author abstract) (52 Refs)

23. TRANSFORMATION OF HAMSTER KIDNEY CELLS BY FRAGMENTS OF BK VIRUS DNA.

Grossi MP, Corallini A, Valieri A, Balboni PG, Poli F, Caputo A, Milanesi G, Barbanti-Brodano G
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J Virol; 41(1):319-325 1982

Hamster kidney cells were transformed, with comparable efficiency, by circular or linear molecules of complete BK virus (BKV) genome and by agarose gel-purified fragments of BKV DNA obtained by single or double digestions with various restriction endonucleases. Only fragments containing the complete early region of BKV DNA displayed transforming activity. Analysis by blot hybridization of the arrangement of viral DNA sequences in a cloned cell line transformed by a 3.8-kilobase fragment, obtained after sequential digestion of BKV DNA with HhaI and BamHI, showed the presence of seven viral integrations into the cellular DNA. Apparently all of the integrated viral molecules contained the entire early region of BKV DNA. Large T antigen, small t antigen, and the 56,000-dalton nonviral Tau antigen were detected in transformed cells by immunoprecipitation. The pattern of integration of viral sequences in transformed cells was constant over many generations. Likewise, large T antigen was always detected in transformed cells at various passage levels. These results may suggest that all of the sequences of the early region coding for large T antigen are required for transformation by BKV. Alternatively, subgenomic segments of the BKV DNA early region may be unable to transform because the appropriate polyadenylation site, necessary to obtain a complete functional transcriptional unit, is removed by the restriction enzyme cleavage. (Author abstract) (34 Refs)

24. IMMUNOLOGIC CROSS-REACTION BETWEEN LARGE T-ANTIGENS OF SV40 AND POLYOMA VIRUS.

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Virology; 116(1):382-387 1982

Serum containing a high titer of antibodies against SV40 T-antigen was produced in rabbits, using D2 protein as immunogen. This protein was purified from cells infected with adenovirus-SV40 hybrid virus Ad2+D2. Anti-D2 serum recognized SV40 large T, but not small T. In addition, it was able to immunoprecipitate polyoma virus large T, demonstrating that these proteins share antigenic determinants. The titer of this antiserum against polyoma virus large T was comparable to the titers of polyoma virus antitumor sera. Anti-D2 serum did not immunoprecipitate polyoma virus middle T or small T antigens. The activity against polyoma virus large T was sensitive to SDS denaturation. (Author abstract) (24 Refs)

25. NEW ANTIGEN INDUCED BY HERPES SIMPLEX VIRUS IN HUMAN TUMORS.

Posevaia TA, Kosiakova NP, Barinskii IF, Kosiakov PN, Pavliuchenkova RP
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Vopr Virusol; (5):597-601 1981

Infection of biopsy specimens of various human tumors with herpes simplex virus was found to induce a new antigen not only in neoplasms of the uterus, cervix, and ovary but also in those of the kidney and bladder. The antigens induced in the cervical carcinoma had the highest complement-fixation activity. (13 Refs) (In RUS)

26. SIMILARITIES AND DIFFERENCES IN THE FC-BINDING GLYCOPROTEIN (GE) OF HERPES SIMPLEX VIRUS TYPES 1 AND 2 AND TENTATIVE MAPPING OF THE VIRAL GENE FOR THIS GLYCOPROTEIN.

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Dept. Medicine, Ohio State Univ. Coll. Medicine, Columbus, OH, 43210
J Virol; 41(1):137-144 1982

We performed affinity chromatography and immunoprecipitation experiments to determine whether cells infected with herpes simplex virus type 2 (HSV-2) expressed a glycoprotein that was functionally and antigenically related to the HSV-1 Fc-binding glycoprotein designated gE. We found that a protein from extracts of HSV-2-infected HEp-2 cells bound specifically to an Fc affinity column and that the electrophoretic mobility of this protein in sodium dodecyl sulfate-acrylamide gels was slightly less than the mobility of HSV-1 gE. Immunoprecipitation experiments performed with an antiserum prepared against HSV-1 gE revealed that (i) extracts from HSV-2-infected cells contained a glycoprotein that was antigenically related to HSV-1 gE; (ii) the electrophoretic mobility of the HSV-2 gE was indistinguishable from the mobility of the HSV-2 Fc-binding protein; (iii) the antiserum reacted with both newly synthesized transient forms and stable fully

processed forms of both HSV-1 gE and HSV-2 gE; and (iv) the transient and stable forms of HSV-2 gE all had lower electrophoretic mobilities than their HSV-1 counterparts. Electrophoretic analyses of gE precipitated from extracts of HEp-2 cells infected with two sets of HSV-1 x HSV-2 intertypic recombinant viruses suggested that the gene for gE is located at the right end of the HSV genome (0.85 to 0.97 map units) in the unique portion of the S component. (Author abstract) (20 Refs)

27. EXPRESSION OF HERPES SIMPLEX VIRUS COMMON SURFACE ANTIGENS AND MALIGNANCY BY CLONAL CELLS OF A HERPES SIMPLEX VIRUS TYPE 2-TRANSFORMED LINE.

Kimura S, Okazaki K, Tanaka S, Yoshida N
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Gan; 72(6):834-841 1981

Herpes simplex virus (HSV) type common surface antigens (CSA) were examined by i ndirect immunofluorescence with rabbit antiserum to HSV Type 1 in a clonal hamster cell line 155-4 transformed by HSV Type 2. The tumor formation was examined in hamsters transplanted with various transformed and tumor cells. The examination of subclones derived from 155-4 cell line gave the following results. (1) Thirty subclones were isolated and classified into three phenotypes as to CSA expression: (i) in CSA-positive type (20% of the clones isolated), the number of CSA-positive cells increased soon (5 hr) after seeding at 37 C; (ii) in CSA-inducible type (33% of the clones), the number of CSA-positive cells increased after treatment with actinomycin D (ACT-D, 2 ug/ml), but not without ACT-D; (iii) in CSA-negative type (47% of the clones), the number of CSA-positive cells did not increase after seeding or after ACT-D treatment. (2) In tumor cell lines derived from the parent line and from three representative clones, CSA expressions were similar to that by CSA-negative type. (3) Transformed cells expressing CSA after seeding or after ACT-D treatment formed tumors and metastases less efficiently than cells expressing little CSA in transplanted hamsters. (4) Tumor cell lines formed tumors and metastases more efficiently than transformed cells expressing little CSA in transplanted hamsters. (Author abstract) (17 Refs)

28. CHARACTERIZATION OF HUMAN CELLS PERSISTENTLY INFECTED WITH CYTOMEGALOVIRUS AND EXPOSED TO A CHEMICAL CARCINOGEN.

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Int J Cancer; 29(1):49-55 1982

A non-productive, persistent human cytomegalovirus (CMV) infection was developed in human embryo lung (LU) cells by initially using supraoptimal temperatures to restrict the replication of a recent CMV isolate (76-24). Although CMV replication was observed in some cells within a few wk of shifting the cultures to 37 C and subculturing, CMV cytopathic effects and infectious CMV were not detected with further subculturing during the next 5 wk. CMV-specific nuclear antigens were, however, observed in most cells (designated LU-76-24) for 38 additional culture passages made during the following 12 mo. Although the LU-76-24 cells were morphologically distinct from LU cell cultures carried in parallel as controls, the LU-76-24 were contact-inhibited in spite of a somewhat disoriented growth pattern. Treatment of LU-76-24 cells with 0.05 ug/ml of the chemical carcinogen 4-nitroquinoline 1-oxide (NQO) induced a lytic CMV infection from which a clone of cells (designated LUC-NQO) was isolated. No effect was seen when LU cells were treated with the same dose of NQO. LUC-NQO cells were morphologically altered from LU-76-24 cells and had lost contact inhibition. Even though CMV-specific nuclear antigens were observed in LUC-NQO cells, infectious CMV was not detected in lysates of these cells, nor was CMV rescued by co-cultivation of these cells with susceptible cells or by induction with 5-iodo-2'-deoxyuridine. LUC-NQO, but not LU or LU-76-24 cells, plated with good efficiency in semi-solid medium. The results indicate that long-term, non-productive, persistent CMV infections can be established in vitro and suggest that such cells may be more susceptible than non-infected cells to the action of chemical carcinogens. (Author abstract) (37 Refs)

29. SHOPE FIBROMA VIRUS. I. BIOLOGICAL AND MOLECULAR PROPERTIES OF A CYTOCIDAL AND A NONCYTOCIDAL STRAIN.

Pogo BG, Freimuth P, Stein A
Center for Experimental Cell Biology, Mount Sinai Sch. Medicine, New York, NY, 10029
J Virol; 41(1):97-103 1982

The biological and molecular properties of two strains of Shope fibroma virus (SFV) were compared. SFV-I was highly cytocidal to most of the cell lines tested and produced pocks in the chorioallantoic membrane of chick embryos. By contrast, SFV-W did not produce cytopathic effects in any of the cell lines or in the chorioallantoic membrane, but it induced characteristic foci 3 to 4 days after infection. Both strains produced tumors when inoculated into the skin of susceptible rabbits. Maximal infectivity in BSC-1 cells was reached by both strains between 24 to 48 hr after inoculation. Viral DNA synthesis also took place at the same time, although cells infected with SFV-I incorporated three times more [3H]thymidine than cells infected with SFV-W. Sedimentation analysis and hydroxylapatite chromatography of the two viral DNAs indicated that their mol wt was similar and that both were naturally cross-linked. Digestion with three restriction endonucleases, however, revealed that they had different restriction sites. When SFV-I and vaccinia DNA were compared, the restriction patterns were more alike. Analysis of the virion structural proteins by gel electrophoresis indicated that SFV-I, SFV-W, and vaccinia virus had many polypeptides in common, although there were distinctive differences among the three viruses. Finally, the results of plaque neutralization tests with different antisera showed that SFV-I and SFV-W shared common antigens and that vaccinia antiserum inhibited SFV-I but not SFV-W. We conclude that the SFV-I genome contains information for both cytolysis and tumorigenesis. This unusual virus may be a recombinant between an orthopoxvirus and a leporipoxvirus. (Author abstract) (19 Refs)

30. THE 2.2 KB E1B MRNA OF HUMAN AD12 AND AD5 CODES FOR TWO TUMOR ANTIGENS STARTING AT DIFFERENT AUG TRIPLETS.

Bos JL, Polder LJ, Bernards R, Schrier PI, Van den Elsen PJ, Van der Eb AJ, Van Ormondt H
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Cell; 27(1,part2):121-131 1981

By nucleotide sequence analysis and S1 nuclease mapping we have determined the s tructural organization of early region E1b of Ad12. We have also revised the nucleotide se-

quence of the E1b region of Ad5. Both regions have an identical structural organization and show considerable homology at the nucleotide level. The major tumor antigens (Ad12, 19 and 54 kilodaltons [kd]); Ad5, 21 and 55 kd are encoded in two overlapping reading frames. A single mRNA of 2.2 kilobases codes for both these proteins, depending on which AUG triplet serves as the start codon: the 19-21 kd protein initiates at the 5'-proximal AUG; the 54-55 kd protein initiates at the second AUG in another reading frame. Peptide mapping shows that the small and large tumor antigens do not share common tryptic peptides, in accordance with the nucleic acid sequence data. In addition, the 19-21 kd protein can also be synthesized from a one kilobase mRNA. Finally, the gene for the Ad12 analog of protein IX is characterized. (Author abstract) (48 Refs)

31. SOMATIC CELL HYBRID ANALYSES OF HEMATOPOIETIC DIFFERENTIATION.

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Blood; 58(6):1159-1163 1981

A differentiated cell expresses an entire set of specialized features. Somatic cell hybridization provides a method to examine control of gene regulation. We studied the expression of tissue-specific features in hybrids between human promyelocytes (HL-60) and human Burkitt's lymphoma cells (P3HR-1). Two hybrid lines, HP-1 and HP-2, and 18 hybrid clones were established and confirmed by karyotype, isozyme, and surface antigen analyses. The hybrids extinguished the 10 myeloid (HL-60) features that we examined including myeloid morphology, histochemistry, and functions that included response to colony-stimulating factor and ability to differentiate to granulocytes or macrophages. In contrast, the hybrids synthesized immunoglobulin and expressed Epstein-Barr nuclear, early, and viral capsid antigens similar to the P3HR-1 lymphoid parental line. Results are contrasted to the findings when P3HR-1 lymphocytes are fused to human erythroid-myeloid cells (K562). Taken together, our results suggest that phenotypic differences between human myeloid and lymphoid cells in the hematopoietic lineage involve mutually exclusive programs and may possibly be mediated by the activity of diffusible, transacting molecules. (Author abstract) (28 Refs)

32. RECENT DISCOVERIES ON CELLULAR PROTEINS IN RELATION TO VIRALLY AND CHEMICALLY INDUCED CARCINOGENESIS.

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Lakartidningen; 78(41):3585-3586 1981

Recent studies on the molecular mechanisms of carcinogenesis suggest the existence of a cellular protein ('53K') common to virally and chemically induced cell transformations. This type of protein binds some T-antigens from oncogenic DNA viruses, including large T-antigen from SV40 and Epstein-Barr virus-determined nuclear antigen. Transformation-related proteins from oncogenic RNA viruses are similar to normal cellular proteins. Several of these proteins have phosphorylating activity, and some of them have been found to be protein kinases. Associations of such proteins with the plasma membrane have also been shown. These different connections between various tumor-related proteins and normal cellular proteins suggest the importance of gene determination in transformations. (11 Refs) (In SWE)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

33. ANTIGEN-SPECIFIC MURINE T-CELL LYMPHOMAS: FUNCTIONAL HETEROGENICITY.

Azar Y, Eidelsztein P, Yefenof E, Chriqui E, Katz-Gross A, Kedar E, Ben-Sasson SZ
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Cell Immunol; 65(1):194-200 1981

Two ovalbumin (OVA)-specific helper lymphomas (designated ROT/6.1 and ROT/6.2) were established by transformation of enriched, OVA-immune T cells with the radiation leukemia virus (RadLV). Shortly after establishment these lymphomas provided carrier (OVA)-specific help for anti-hapten antibody response. However, 5 mo later ROT/6.1 lost its OVA specificity and could augment anti-hapten antibody response in the presence of an unrelated carrier. ROT/6.2 retained its antigen-specific helper function over 10 mo of repeated passaging. This OVA-specific helper line inhibited anti-hapten antibody response when given together with an unrelated carrier. Cloning of ROT/6.2 by limiting dilution revealed that only 3 of 10 clones tested had OVA-specific helper activity. None of the clones could induce antigen-specific DTH reaction. The interrelationship between the functional heterogenicity, specificity, and stability of the helper lines is discussed. (Author abstract) (17 Refs)

34. CELL SURFACE ANTIGENS OF X-RAY INDUCED LYMPHOMA: DETECTION AND CHARACTERIZATION USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Allison JP
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Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

The cell surface antigenic mosaic of an x-ray induced lymphoma of C57BL/6 mice has been examined using conventional and monoclonal antibodies. The tumor cells display four glycoproteins related to murine leukemia virus (MuLV) - two env and two gag gene products. Immunization of syngeneic mice with tumor cells elicited formation of antibodies to only one of the two MuLV env proteins. Analysis with monoclonal antibodies revealed that this antigen was antigenically related to ecotropic MuLV. One hybr idoma clone, designated 124-40, produced by fusion of spleen cells from C6XL-immunized BALB/c mice with P3 myeloma cells, secreted monoclonal antibodies (McAb) which reacted with tumor cells, but not with normal lymphoid cells. The tumor associated antigen reative with McAb 124-40 was found to be a glycoprotein with subunit mol wt of approx 40 Kd, and was structurally and immunologically distinct from MuLV antigens on the tumor cells. The antigen was not found on adult spleen, thymus, bone marrow, or lymph node cells, nor on fetal thymus or spleen. Two additional x-ray lymphoma lines, as well as three spontaneous leukemias of AKR mice, were also unreactive with McAb 124-40. Administration of the McAB 124-40 to tumor-bearing mice resulted in a slight increase in survival time. The therapeutic effect was greatly enhanced by administration of McAb conjugated to the cellular toxin pokeweed antiviral protein. (no Refs)

35. GROWTH AND INFECTIVITY TITRATION OF VIRULENT INFECTIOUS BURSAL DISEASE VIRUS IN ESTABLISHED CELL LINES FROM LYMPHOID LEUKOSIS TUMORS.

Yamaguchi S, Imada T, Kawamura H
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Avian Dis; 25(4):927-935 1981

The most suitable cell culture for growth of virulent infectious bursal disease virus (IBDV) was investigated as was the possibility of infectivity titration and serological tests with cell cultures. In the study of susceptibility to the virulent (wild) and attenuated IBDV by detection of fluorescent antigen in inoculated cells, lymphoblastoid cell lines LSCC-BK3 (LBK) and LSCC-CU10 were susceptible to both, while line LSCC-1104-B-1 was susceptible only to the attenuated form. The LBK line was the most susceptible line to any IBDV and was used in further experiments. Two lymphoid leukosis and two MD cell lines were refractory to growth of any type of IBDV. When the J1 strain of virulent IBDV was inoculated into LBK cells, intra- and extracellular viruses began logarithmic increase between 4 and 8 hr postinoculation and reached 106.3-7.3 TCD50/0.1 ml, respectively, at 72 hr. Infectivity titration and serum-neutralization tests of virulent IBDV were possible with LBK cells. (13 Refs)

36. IN VITRO PHOSPHORYLATION OF MURINE LEUKEMIA VIRUS PROTEINS: SPECIFIC PHOSPHORYLATION OF PR65GAG, THE PRECURSOR IN THE INTERNAL CORE ANTIGENS.

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Virology; 116(1):181-195 1982

In vitro phosphorylation of Nonidet P-40 disrupted murine leukemia virus with [gamma-32P]ATP showed that Pr65gag, which is present as a relatively minor component (14% of total Coomassie blue-stained virus proteins), was the major (80% labeling) phosphorylated species. A small amount of 32P label (ie, 3-9%) was associated with proteins whose mobility on sodium dodecyl sulfate-polyacrylamide gel electrophoresis was the same as Pr40gag, p12, and p10. In contrast, long-term (20 hr) in vivo phosphorylation with [32P]orthophosphate showed that p12 was the most highly phosphorylated viral protein species. In neither case did we find any label associated with the major virion proteins, p30, p15, or gp70. These results suggest that phosphorylation is specific for certain viral proteins and, further, that if Pr65gag is packaged as an uncleaved polyproteins into virions it remains relatively unphosphorylated. We have also found that the kinase activity which phosphorylates Pr65gag in vitro is tightly associated with immature core subparticles and can phosphorylate the exogenous substrate phosvitin. The same or an additional kinase activity can also be detected in the soluble fraction of detergent-disrupted virus using endogenous viral proteins or phosvitin as substrate. Based on an analysis of the tryptic peptide patterns of pPr65gag phosphorylated in vitro and in vivo, it appears that the in vitro phosphorylation of Pr65gag occurs at serine residues which are identical to or similar to those found for pPr65gag in vivo, ie, on pp12, as well as at another site. This other site is also probably on p12 since in vitro phosphorylated pPr65gag, when cleaved in vitro by the murine Pr65gag proteolytic factor, produces as its initial product a phosphorylated band that has the mol wt of pPr27gag and the antigenic determinants of p15 and p12. (Author abstract) (24 Refs)

37. SYNTHESIS OF A VIRAL PROTEIN WITH MOLECULAR WEIGHT OF 30,000 (P30) BY LEUKEMIC CELLS AND ANTIBODIES CROSS-REACTING WITH SIMIAN SARCOMA VIRUS P30 IN SERUM OF A CHRONIC MYELOID LEUKEMIA PATIENT.

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Cancer Res; 42(2):681-686 1982

We studied a patient with a Philadelphia chromosome-positive chronic myeloid leukemia, who died in relapse after multiple transfusions and grafting with bone marrow from his monozygotic twin brother (referred to as 'donor' in this paper). We present data indicating that this patient may have had a retrovirus infection and that this virus is related to the group of exogenous primate Type C retroviruses. Antibodies to simian sarcoma virus (SSV) mol wt 30,000 protein (p30) but not endogenous feline virus RD-114 could be found in patient but not donor serum. Patient but not donor cells were able to actively synthesize a p30 protein that could be precipitated with patient serum and rabbit anti-SSV p30 but not with donor serum or rabbit anti-RD-114 p30. Patient p30 resembles SSV p30 but not RD-114 p30 in peptide mapping by limited proteolysis and subsequent slab gel electrophoresis. Patient but not donor cells were able to actively synthesize a mol wt 78,000 protein that could be precipitated with goat anti-SSV. An enzyme with properties of reverse transcriptase was increased 30-fold in patient cells when compared with donor and other control cells. Related to the presence of widespread infectious agents may be the finding that, in the course of the patient's disease, donor serum showed increasing amounts of possibly immunoregulatory antibodies, reactive with autologous and, more effectively, with patient-derived cell membrane mol wt 80,000 protein (a possible idiotypic receptor structure) and mol wt 94,000 protein (a T-cell alloantigen). (Author abstract) (31 Refs)

38. ASSOCIATION OF MURINE LEUKEMIA VIRUS GAG ANTIGEN WITH EXTRACELLULAR MATRICES IN PRODUCTIVELY INFECTED MOUSE CELLS.

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Virology; 116(1):306-317 1982

The gag gene of murine leukemia virus (MuLV) encodes a nonstructural glycosylated polyprotein which appears at the cell surface, in addition to the polyprotein precursor for the virion internal structural proteins. The surface localization of gag nonstructural protein is reported here. Immunofluorescent staining of unfixed monolayers of Moloney MuLV-infected NIH/3T3 cells using anti-p30 serum as the primary antibody revealed an unusual pattern of gag antigen at the attached cell surface: highly organized cable-like structures. Stained cable-like structures were also observed in regions lacking cells or cell processes, which suggested that extracellular gag antigen may be associated with extracellular matrices. This was supported by the fact that detergent treatment of cell monolayers in a manner designed to removed intact cells but preserve extracellular matrices did not affect the cable-like anti-p30 staining patterns. Immunofluorescent staining with anti-gp70 serum revealed a different pattern than the anti-p30 staining, which indicates that surface gag antigen and envelope glycoprotein are not physically associated at the cell surface. Similar staining patterns were observed in mouse cells productively infected with a different strain of MuLV (AKR), and in mink cells

productively infected with a mink cell focus-inducing (MCF) derivative of Rauscher MuLV. (Author abstract) (30 Refs)

39. H-2D CONTROL OF RADIATION LEUKEMIA VIRUS INDUCED NEOPLASIA: EVIDENCE FOR INTERACTION OF VIRAL AND H-2 GENOMIC INFORMATION.

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Transplant Proc; 13(4):1858-1862 1981

Integration of viral genetic information occuring at or near H-2D and resulting in deregulation of transcription of H-2D genes, as the possible mechanism by which radiation leukemia virus (RadLV) infection increases H-2D expression in the thymus, is discussed. Intrathymic inoculation of RadLV to mice in varied genotypes leads to increased H-2D expression as long as their genotype is Fv-1b. The inductive mechanism augmenting H-2Dd synthesis does not operate in a trans mode. Thymocytes from susceptible and resistant mice were exposed to particular agents in vivo. No agent, except soluble extracts from RadLV-infected thymocytes, was capable of selectively changing H-2D antigen expression on thymocytes of resistant but not susceptible mice. Blocking virus integration prevents RadLV-induced changes in H-2D expression. Experiments showed that ethidium bromide and fluoro-deoxyuridine (FUdR) inhibit H-2D antigen deregulation, while thymidine is able to block the effects of FudR. RadLV is able to induce H-2D increases as early as 12 hr after inoculation. The integration of proviral DNA into host genomic material requires a minimum of 6 hr. The inability of soluble extract from resistant thymocytes older than 3-5 wk past RadLV infection to increase H-2D expression vs the fact that in resistant mice H-2D remains elevated for at least 12 wk after virus infection implies that the virus-coded information once integrated can continue to deregulate H-2D antigen expression even in the absence of provirus synthesis. (14 Refs)

40. SPECIFICITY OF SYNGENEIC MONOCLONAL ANTIBODIES AGAINST CELL SURFACE ANTIGENS ON CHEMICALLY INDUCED MOUSE FIBROSARCOMAS.

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Transplant Proc; 13(4):1762-1764 1981

Development and characterization of 16 monoclonal antibodies (McAb) against tumor-specific transplantation antigens (TSTA) are reported. McAb were developed by immunizing C57BL/6 and BALB/c mice with their own syngeneic, chemically induced fibrosarcomas bearing unique TSTA; the formation of hybridomas followed. Radioimmunoassays were carried out with a large panel of normal cells, tumor cells, and ecotropic and xenotropic murine leukemia viruses (MuLV). Competitive binding assays used tumor cells and MuLV against well-characterized anti-MuLV gp70 and p15(E) McAb. No highly restrictive tumor specificity was found for any of 16 McAb tested. All McAb showed either MuLV-dependent or MuLV-independent cross-reactivity with several mouse tumor strains. Results obtained with five McAb are tabulated. Reactions to anti-MuLV indicated that M3, PC11, and CS-1 tumor strains express gp70 and p15(E) antigens of ecotropic and/or xenotropic viruses on the cell surface. McAB L1 and 4B1 were specific for tumors bearing MuLV antigens. The 4B1 McAb was specific for a molecule similar or identical to the gp70a epitope of ecotropic MuLV. Three McAb showed tumor reactions independent of MuLV antigens. Failure to produce a tumor-specific McAb may be due to differences in T and B cell function or to sampling luck. (9 Refs)

41. HERITABLE DIFFERENCES AMONG GP70-LIKE MOLECULES ON C3H ULTRAVIOLET LIGHT-INDUCED FIBROSARCOMAS.

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Transplant Proc; 13(4):1782-1786 1981

Tumor antigens found on UV-induced fibrosarcomas (UV-FS) in C3H mice were studied. C3H/HeN mice were immunized with UV-FS cells implanted by trocar. Syngeneic antisera (AS) were obtained from the mice. The AS contained antibodies (AB) specific for the immunizing tumor and AB that cross-reacted with other C3H FS lines. Immunoprecipitation of 125I-labeled lysates of six different UV-FS lines detected the consistent presence only of molecules of mol wt 70,000-90,000 dalton. Although resolution of the complexity of the molecules was not possible with one-dimensional gel electrophoresis (GE), two-dimensional GE showed that the tumor molecules recognized by the AS had heterogeneous charges and heterogeneous mol wt. Heterogeneity was possible due to variations in glycosylation, amino acid sequences, or proteolytic processing of precursor molecules. Molecules apparently identical to those precipitated by syngeneic AS were precipitated by goat anti-Rauscher leukemia virus gp70 and goat anti-BALB/c virus-2 gp70 sera. Within a tumor cell line the patterns of heterogeneous molecules in the 70,000-90,000 mol wt range were constant and independent of in vivo or in vitro passage generation. Among various tumor lines considerable variations were apparent. Analysis of molecules from UV-FS suggests that the tumors produce at least two distinct gp70-like molecules, one that is the C3H ecotropic viral gp70 , and one of lower mol wt that is substantially different from ecotropic gp70. (20 Refs)

42. SPECIFIC ANTIGENS ON METHYLCHOLANTHRENE-INDUCED TUMORS OF MICE.

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MRC Lab. Molecular Biology, Hills Road, Cambridge, CB2, 2QH, England
Transplant Proc; 13(4):1759-1761 1981

Development of monoclonal antibodies to B10/MC6A (6A) mouse sarcoma is reported. A B10 mouse was immunized with tumor cells. Spleen cells from the immunized mouse were fused with myeloma cells to form hybrid cells. Hybrids producing antibodies to tumor-specific transplantation antigens (TSTA) were selected by assays using cells from lines 6A and B10/MC6B (6B: a tumor line not cross-reacting with 6A). One monoclonal antibody designated 4B1 was tested for specificity for tumor line 6A. Although 4B1 showed 10-20% cross-reaction in transplantation assays, 6B did not cross-react with 6A. Assays using B6 and BALB/c tumors detected several 4B1-positive tumor lines, two of which showed cross-protection. An assay using immunized B10 mice showed that immunization with cells from either of two 4B1-positive tumor lines protected the mice against challenge by 6A cells; cells from a 4B1-negative line did not. Evidence suggests a correlation between the 4B1 antigen and the TSTA of the 6A tumor line. The molecule carrying 4B1 specificity is a protein with approx mol wt of 70,000; the protein carries the a-epitope of the gp70 retrovirus envelope protein, which is recognized by the previously reported antibody anti-gp70 16B7. Both the 16B7 and 4B1 anti-

gens appear on the same cells, and each blocks binding of the other. Findings suggest that specificity of TSTA is carried on gp70-like molecules. (7 Refs)

43. INCORPORATION OF INFLUENZA VIRUS ANTIGENS IN AVIAN SARCOMA VIRUS ENVELOPE.

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Vopr Onkol; 27(10):63-67 1981

The mixture of influenza virus and pseudotype of Rous sarcoma virus RSV (PAB-A) grown in chick embryos or cell culture of chick fibroblasts produces a progeny which can be partially neutralized by a heterologous immune serum. The fraction of viral particles, the transformation activity of which is susceptible to suppression by both homologous anti-RSV (PAB-A) and heterologous serum, immune to influenza virus, amounts to approximately 20%. After passage, 57 these particles lose this property which suggests a non-genetic character of the phenomenon. Hence, dual infection results in phenotypic mixing and formation of particles with nucleoprotein of RSV (PAS-A) which contain antigens of avian sarcoma and influenza viruses in their envelopes. (Author abstract) (8 Refs) (In RUS)

44. BIOCHEMICAL CHARACTERIZATION OF MURINE BONE MARROW GP71.

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FEBS Lett; 135(1):43-48 1981

AKR-like glycoprotein 71 (gp71) purified from mouse bone marrow was studied and compared structurally with some viral proteins. The purification of bone AKR-murine leukemia virus (AKR-MuLV) gp71 is described. Immunoprecipitation was performed on both viral and bone marrow gp71. Tryptic peptide maps of bone marrow, AKR-MuLV and Balb (X) gp71 are presented. A distinct pattern of spot distribution was observed in each case. The comparison of the bone marrow antigens with both viral products showed that the tissue gp71 resembles the xenotropic map more than the AKR map; the NIH Swiss mouse bone marrow protein also resembled the xenotropic map. Thus the antigenic relation was not accompanied by clear structural similarity. Bone marrow antigen and viral gp71 showed similar elution behavior in Sepharose columns and migrated to the same position in sodium dodecyl sulfate-polyacrylamide gels suggesting that the bone marrow antigen is a lso a glycoprotein of 70,000-71,000 mol wt. The AKR gp-71-like antigen accounted for 180 and 140 nanog/mg total bone marrow protein in Balb/c and NIH Swiss mice, respectively. (14 Refs)

45. EARLIER APPEARANCE OF MURINE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENS IN DUCT-ALVEOLUS NODULES INDUCED BY TRANSPLANTATION OF FETAL SALIVARY MESENCHYME INTO C3H MOUSE MAMMARY GLANDS.

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Gan; 72(6):982-987 1981

Mammary epithelium of adult C3H mice in contact with fetal salivary mesenchyme took morphogenetically a salivary gland-like pattern of growth and developed a hyperplastic nodular mass at the site of transplantation. When murine mammary tumor virus-bearing C3H mice were treated in this way, early development and high incidence of mammary cancer were observed from these nodules compared to unstimulated mammary glands of the same host. Since it is known that murine mammary tumor virus plays a major role in mammary tumor development, the viral antigens in these hyperplastic nodules were examined by means of the immunofluorescence technique. As early as 2 wk after mesenchyme transplantation, the antigens were observed in the ductular or alveolar structure of these nodules, while surrounding normal tissues were not stained. Positive fluorescence was also observed in the mammary tumors that developed from these stimulated nodules. These results strongly suggested the involvement of murine mammary tumor virus in the early development of mammary cancer induced by fetal mesenchyme transplantation. (Author abstract) (12 Refs)

46. IDENTIFICATION OF A 39,000-DALTON PROTEIN IN CELLS TRANSFORMED BY THE FBJ MURINE OSTEOSARCOMA VIRUS.

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Virology; 116(1):221-235 1982

Two components of the FBJ murine osteosarcoma virus complex have been isolated separately in tissue culture; the FBJ murine leukemia virus (FBJ-MLV) by dilution and the FBJ murine sarcoma virus (FBJ-MSV) by the establishment of nonproducer transformed rat cells. Analysis of these cells using MLV antisera indicated that there were no new proteins related to viral structural proteins specifically associated with the presence of the FBJ-MSV genome. The FBJ-MSV nonproducer cells were used to induce tumors in syngeneic and allogeneic F1 rats. Sera from tumor-bearing rats were examined for activity against FBJ-MSV-specific antigens. A number of sera were found to precipitate a 39,000-dalton protein, p39, from several producer and nonproducer FBJ-MSV transformed rodent cells, but not from cells transformed by other strains of MSV or cells infected with MLV. Precipitation of p39 was not blocked by the presence of excess viral proteins, indicating that p39 is not related to the viral structural proteins. This conclusion was confirmed by methionine tryptic peptide analysis which showed that the fingerprint of p39 was distinct from those of the viral gag or env gene proteins. The data demonstrate the presence of a unique antigenic protein, unrelated to the MLV proteins, in FBJ-MSV transformed cells. (Author abstract) (41 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

47. CELL-MEDIATED IMMUNITY TO HERPES SIMPLEX VIRUS: RECOGNITION OF TYPE-SPECIFIC AND TYPE-COMMON SURFACE ANTIGENS BY CYTOTOXIC T CELL POPULATIONS.

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Infect Immun; 34(3):795-803 1981

In this communication, we examine the specificity of anti-herpes simplex virus (HSV) cytotoxic T lymphocytes (CTL). Serological studies of the two related HSV serotypes (HSV-1 and HSV-2) have revealed both type-specific and cross-reactive antigenic determinants in the viral envelope and on the surface of infected cells. by analysis of cytotoxicity of CTL generated in vitro by restimulation of splenocytes from mice primed with one or the other HSV serotype, the recognition of both type-specific and cross-reactive determinants on infected target cells by anti-HSV CTL was detectable. Thus, effector cells generated by priming and restimulating with the same virus recognized both type-specific and cross-reactive determinants on target cells infected with the homologous virus, but only cross-reactive determinants on target cells infected with the heterologous HSV serotype. CTL generated by restimulation with the heterologous virus were capable of recognizing only the cross-reactive determinants on either HSV-1-or HSV-2-infected target cells. These results indicate that two subpopulations of CTL exist in a population of anti-HSV immune spleen cells - those which recognize type-specific determinants and those specific for cross-reactive antigenic determinants present on the surface of HSV infected cells. The type-specific subset of anti-HSV CTL was shown to recognize the gC glycoprotein of HSV-1 infected target cells. In addition to the gC glycoprotein, at least one other type-specific surface antigen was also recognized by anti-HSV CTL in addition to the cross-reactive determinants recognized by anti-HSV CTL. (Author abstract) (23 Refs)

48. VARIATION IN MHC ANTIGENIC PROFILES OF TUMOR CELLS AND ITS BIOLOGICAL EFFECTS.

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Immunol Rev; 60:85-127 1981

Four kinds of Gross virus leukemias were studied; long transplanted cell lines derived from spontaneous AKR mice leukemia K36 maintained and propagated both in vivo and in vitro, tumor cel l line K-GV induced in female BALB/K mice, newly isolated spontaneous AKR leukemias, and tissue culture clones established from AKR spontaneous leukemias. Absence of the H-2Kk gene product from the K36 and K-GV leukemias was noted. Cellular immunological tests and immunochemical analysis performed showed that Gross virus T cell toxicity is H-2Kk restricted. There is a direct correlation between the representation of the H-2Kk product on the tumors and the ability to lyse them with T cells in vitro. Tumors with decreased or absent H-2Kk tend to grow in mice. Biological consequences of losses and gains of major histocompatibility system (MHS) were studied. It was suggested that similar to immunoglobulins more than one gene may encode individual MHS molecules. (82 Refs)

49. THE IMMUNOREGULATORY CHARACTERISTICS OF THE LACTIC DEHYDROGENASE VIRUS (LDV), A COMMON CONTAMINANT OF TUMORS.

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Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel
Cell Mol Biol; 27(2/3):83-96 1981

A tumor-enhancing and antibody increasing spleen cell-associated factor originating in Lewis lung carcinoma (3LL)-bearing C57BL/6 mice was identified as the lactic dehydrogenase virus (LDV). A potent immunoregulating factor was obtained only following the inoculation of LDV-infected but not LDV-free tumor cells. The observed augmentation of humoral responses by an acute infection with LDV was found to be fully correlated with the ability of the virus to replicate and establish a persisting infection in the host. LDV caused an augmented humoral response in all mouse strains tested (causing a lifelong viremia), but failed to influence the humoral response in rats, which are an LDV-resistant species. We found that although an infection with LDV causes a polyclonal B-cell activation it does not affect all of the different B-cell clones and in the presence of a specific antigenic stimulus it preferentially triggers the IgG2 subclass of antibody-secreting B cells. An acute LDV infection causes a substantial suppression of cell-mediated immunity functions and a delayed thyroid allograft rejection was demonstrated in infected mice. Since mononuclear phagocytes, which are the target cells of LDV, play an important role in cellular immune responses, we tested the immunogenic antigen-presenting capacity of LDV-infected macrophages, using a system in which in vitro reactivation of memory T cells is dependent upon effective specific antigen presentation by macrophages. We found that the antigen presentation capacity of macrophages from acute LDV-infected mice is impaired. These results may contribute to a better understanding of the ways in which mammalian RNA viruses may act as immunomodulators. (Author abstract) (42 Refs)

50. H-2 RESTRICTION OF THE T CELL RESPONSE TO CHEMICALLY INDUCED TUMORS: EVIDENCE FR OM F1 TO PARENT CHIMERAS.

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J Immunol; 128(1):263-268 1982

It has been well established that T cells that react to tumor antigen on virus-induced tumors must share H-2D or H-2K specificities with the tumor. It has been impossible to perform similar studies with chemically induced tumors because each chemically induced tumor expresses a unique tumor antigen that cannot be studied in association with other H-2 types. This study provides evidence that H-2 recognition is also necessary for recognition of chemically induced tumors. We have found that F1 to parent chimeras preferentially recognize chemically induced tumors of parental H-2 type. C3H/HeJ and C57BL/6 mice were lethally irradiated and restored with (C3H x C57BL/6)F1 hybrid bone marrow. The F1 to C3H chimera but not the F1 to C57BL/6 chimera was able to respond to a C3H fibrosarcoma in mixed lymphocyte-tumor cell culture and also to neutralize the tumor in an in vivo tumor neutralization assay. On the other hand, the F1 to C57BL/6 chimera but not the F1 to C3H chimera was able to kill the C57BL/6 lymphoma EL4 in an in vitro cytotoxicity assay. Both chimeras were tolerant to C3H and C57BL/6 alloantigens but could respond normally to Con A and to BALB/c spleen cells in mixed lymphocyte cultures and cytotoxicity assay. Thus, it appears that the requirement to recognize tumor antigen in asso-

ciation with major histocompatibility antigen is not restricted to virus-induced tumors but may apply to many types of neoplasms. This should be considered in all studies of immune reactivity against tumors and in designing protocols for immunotherapy. In addition, it is possible that changes in H-2 expression on a tumor may allow that tumor to escape the host's immune response. (Author abstract) (37 Refs)

51. GENERATION IN VITRO OF HLA-RESTRICTED EB VIRUS-SPECIFIC CYTOTOXIC HUMAN T CELLS BY AUTOLOGOUS LYMPHOBLASTOID CELL LINES: THE ROLES OF PREVIOUS EB VIRUS INFECTION AND FOETAL CALF SERUM.

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Int J Cancer; 29(1):41-48 1982

The cytotoxic response of human lymphocytes to the autologous lymphoblastoid cell line (LCL) was investigated with five Epstein-Barr virus (EBV)-seropositive and four seronegative donors and an additional donor who seroconverted during the course of the study. Without exception, the cytotoxic T cells generated in 7-and 14-day LCL-stimulated cultures from seropositive donors were strongly lytic for the autologous LCL. Overall, the cytotoxic T cells generated in cultures from seropositive donors showed a striking preferential lysis of the autologous LCL and cross-reactive killing of allogeneic LCL target cells mat ched for certain HLA-B antigens. Lysis of the K562 line was consistently negligible. In comparison to the considerable self-preferred lysis obtained with T cells from LCL-stimulated cultures, the level of autologous killing by T cells generated in control unstimulated cultures was relatively low. The cytotoxic patterns obtained with cytotoxic T cells generated in cultures from seronegative donors were markedly different from those obtained with seropositive donors. The level of autologous killing by T cells harvested from LCL-stimulated cultures was considerably lower than that obtained with seropositive donors and often did not increase above that seen in control cultures, except at the highest stimulatory dose. Moreover, preferential lysis of the autologous LCL target cells by T cells from LCL-stimulated cultures was essentially due to the fetal calf serum (FCS)-induced cytotoxicity, and there was no obvious HLA-antigen-restricted killing of allogeneic target cells. Lysis of K562 target cells was generally more pronounced at the highest level of stimulation than that observed with seropositive donors. The distinctive cytotoxic T-cell response patterns observed with the seropositive and seronegative donor cultures were both observed with cultures from an individual donor who was tested before and after infectious mononucleosis. With LCL-stimulated cultures from seropositive donors, the cytotoxic T-cell response to autologous LCL is predominantly directed against EBV-associated antigens and is HLA-antigen restricted. In contrast, with seronegative donor cultures, the cytotoxic T-cell response is primarily due to FCS-induced cytotoxicity, although a response against other LCL-associated antigens may be superimposed in cultures stimulated with high levels of autologous LCL. (44 Refs)

52. H-2KB MUTATIONS LIMIT THE CTL RESPONSE TO SV40 TASA.

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J Immunol; 128(1):243-246 1982

The cytotoxic T lymphocyte (CTL) responses directed towards SV40 tumor-associated specific antigen (TASA) in nine strains of spontaneously arising Kb mutant mice were analyzed. All nine mutants generated normal level of H-2Db-restricted response, but the K-end-restricted CTL response varied. B6.C-H-2bm1 (bm1) did not produce K-end-restricted SV40 TSA-specific CTL upon immunization, and SV40-transformed bm1 cells were not lysed by intra-H-2 recombinant Kb [B10.A(5R)] CTL. Nonreciprocal cross-reactive lysis was seen between B6-H-2bm8 (bm8) and B10.A(5R). Strain B6-H-2bm8 mice produce highly specific Kbm8-restricted CTL that lyse SV40-transformed bm8 cells (Kbm8SV) but not B10.A(5R) target cells (K5RSV), although Kbm8SV targets can be partially lysed by B10.A(5R) CTL. The other seven Kb mutants cross-react with B10.A(5R). These expe riments definitively show that genes mapping to the K and/or D region directly control the H-2-restricted CTL response to SV40 TASA. (Author abstract) (24 Refs)

53. INHIBITION OF THE YC8 LYMPHOMA GROWTH BY ALLOIMMUNIZATION WITH NORMAL CELLS.

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Transplant Proc; 13(4):1906-1909 1981

Effects of alloimmunization with normal mouse lymphoid cells were studied in relation to the resistance of BALB/c mice to the growth of syngeneic Moloney virus-induced lymphoma YC8, previously shown to lack detectable amounts of alien H-2 antigens. Alloimmunization of BALB/c mice with normal lymphoid cells elicited a strong resistance to otherwise lethal doses of YC8 cells; the phenomenon was particularly evident and reproducible in mice immunized either with B10.A, B10.D2, or pool 5 lymphoid cells. Neither H-2 differences nor route of immunization affected the response. Alloimmunization with tissues of a single strain were less effective in reducing the growth of other syngeneic lymphomas and sarcomas. However, pool immunization with tissues of five different strains significantly retarded the growth of the BALB/c radiation-induced lymphoma RL(male)1, and of the urethan-induced BALB/c lymphoma Ur-1. The presence of effectors capable of killing YC8 cells in alloimmune BALB/c mice was examined in vitro. Efficacy of B10.D2 or DBA/2 but not of B10.A immunization in inducing anti-YC8 effectors indicated that in vivo and in vitro systems may have different requirements for the immune response. Immunity to YC8 was restricted by gene products of the major histocompatibility complex, possibly the Kd-IEd regions, in only the in vitro environment. The mechanism by which alloimmune prevention operates may involve a cross-reaction between antigens of normal allogeneic lymphocytes and antigens expressed by the tumor, natural killer-like cells, viral antigens, or alloreactivity. (14 Refs)

54. INCREASED RESPONSES TO LYMPHOKINES ARE CORRELATED WITH PRELEUKEMIA IN MICE INOCULATED WITH MOLONEY LEUKEMIA VIRUS.

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Proc Natl Acad Sci USA; 78(12):7712-7716 1981

In various mouse strains, inoculation with Moloney leukemia virus results in the establishment of an acute viremia which in most cases is followed by the induction of leukemia. Also associated with the viremia is the development of a chronic cellular immune response detectable in vitro by the ability of viral proteins to induce splenic lymphocyte proliferation. Previous

studies have demonstrated that, in the absence of this cellular immune response, leukemia does not develop irrespective of whether vire mia is present. In vitro proliferative responses to antigens involve the nonspecific response of various subpopulations of lymphocytes to lymphokines produced by antigen-specific Thy 1+, Lyt 1+,2-lymphocytes. The studies presented here concern the effects of a chronic immune response in viremic mice on the frequency of lymphocytes capable of responding to lymphokines in vitro. The data demonstrate that the number of responsive lymphocytes is increased 30-to 100-fold in preleukemic mice and that such increases are dependent upon the induction of an immune response in viremic mice. The role of this altered immune response in leukemia is discussed. (Author abstract) (18 Refs)

55. QUANTITATIVE VARIATIONS IN THE EXPRESSION OF H-2 ANTIGENS ON MURINE LEUKEMIA VIRUS-INDUCED TUMOR CELLS CAN AFFECT THE H-2-RESTRICTION PATTERNS OF TUMOR-SPECIFIC CYTOLYTIC T LYMPHOCYTES.

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J Exp Med; 154(6):1795-1810 1981

Expression of major histocompatibility antigens (H-2) Kd and Dd was quantified in three different leukemia cell lines induced by Gross murine leukemia virus (MuLV) in BALB/c (H-2d) mice. Preferential recognition of Gross MuLV-induced tumor antigen with H-2Kk or H-2Dd antigen by tumor-specific cytotoxic T lymphocytes (CTL) from BALB/c mice was correlated with the quantitations. The three BALB/c tumor lines differed in amount of H-2Kd and H-2Dd antigens expressed on the cell surface; the variations were reflected in quality as target cells to Gross MuLV-specific CTL from BALB/c mice. The results indicated that restriction of tumor-specific CTL activity by H-2 can be directed at the target cell level by the quantitative modulation of H-2K or H-2D antigen expression; separate tumors induced by the same MuLV in the same or in H-2-congeneic strains of mice may vary in absolute amount of H-2K or H-2D antigen expressed on the cell surface. (35 Refs)

56. EFFECT OF THYMECTOMY ON DEVELOPMENT OF LUCKE RENAL ADENOCARCINOMAS IN VIRUS-INFECTED LEOPARD FROG TADPOLES.

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JNCI; 68(1):133-138 1982

Thymectomy of very young leopard frog (Rana pipiens) larvae dramatically reduced in vitro lymphocyte responses to the mitogen phytohemagglutinin-P and prolonged survival of Lucke tumor alloimplants. However, tumor incidence in premetamorphic or metamorphosing frogs that had received injections as embryos of Lucke tumor herpesvirus (LTHV) was the same in thymectomized and normal immunocompetent animals. This result suggests that T-cell-mediated cytotoxicity does not prevent development of Lucke tumors in immunocompetent larvae and that if tumor-specific transplantation antigens appear, they may induce tolerance rather than destructive immunity in normal LTHV-infected larvae. (Author abstract) (37 Refs)

57. DIFFERENTIAL REGULATION OF H-2 ANTIGEN EXPRESSION IN TUMORS AND ITS BIOLOGIC CONSEQUENCES.

Schmidt W, Alonso A, Leben L, Festenstein H, Martin WJ, Meruelo D, Schirrmacher V, Rajan, Lennox ES, Bach FH, Rogers MJ
Dept. Virology FB23, Justus-Liebig-Univ., D-6300 Giessen, W. Germany
Transplant Proc; 13(4):1814-1818 1981

Variations in H-2 antigen expression and their effects on immune response in 10 mouse leukemia cell lines were studied. Cell lines were derived from spontaneous leukemias in AKR mice and AKR/Gross murine leukemia virus (MuLV)-induced leukemias in BALB.K(H-2k) mice, and were designated K36.16, k-GV, 110, 344, 389, 424, 339, 365, 369, and 422. Assays of complement-dependent cytotoxicity indicated that expression of both H-2Kk and H-2dk antigens was slightly increased in 365 and highly increased in 339 and 369. Expression of H-2.Kk antigen was reduced and expression of H-2Dk was normal in 110 and 424. Expression of H-2Kk was absent, and expression of H-2Dk was normal or reduced in K36.16, k-GV, 334, 389, and 422. Loss of H-2Kk, when observed, was consistent within cell lines in vivo and in vitro. Results of cytotoxicity assays were confirmed by similar results with absorption and immunofluorescence assays. Labeling experiments with [3H]- or [14C]-arginine indicated that differences in H-2Kk and H-2Dk expression are reflected at the level of biosynthesis and are not due to turnover or blocking at the cell surface. Results of stimulation of cytotoxic effector cells (CTL) with k-GV or 369 tumor cells showed that cytolysis of cells lacking H-2Kk is low; H-2Kk is apparently important for H-2-restricted cytolysis of cells by CTL sensitized against viral antigens. Changes in H-2Kk expression may play an important role in the development of leukemia. (12 Refs)

58. HUMAN HYBRIDOMAS (MEETING ABSTRACT).

Croce CM
The Wistar Institute of Anatomy and Biology, 36th Street at Spruce, Philadelphia, PA, 19104
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Human myeloma cells were mutagenized and selected for deficiency in hypoxanthine phosphoribosyltransferase (HPRT). HPRT deficient mutants were then fused with human lymphocytes derived from patients responding to viral antigens and self antigens. Hybridomas secreting anti-viral antibodies and auto-antibodies were obtained. The use of the human hybridoma technology to study human autoimmune diseases will be discussed. (no Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

59. IN VITRO AND IN VIVO INHIBITION OF MYXOMA VIRUS BY TREATMENT WITH PHOSPHONOACETIC ACID.

Goodrich JM, Lee KW, Hinze HC
Rush Medical Coll., Chicago, IL
Arch Virol; 70(2):157-164 1981

Both myxoma and fibroma viruses were found to be sensitive in vitro to the effects of phosphonoacetic acid. Detectable

myxoma virus replication was inhibited at a drug concentration of 100 ug/ml. Fibroma virus replication was inhibited at a concentration of 500 ug/ml. Because of this difference in sensitivity, myxoma virus was used to infect rabbits to test the efficacy of phosphonoacetic acid in the treatment of a systemic viral disease. Rabbits were given 400 mg kg-1 day-1 of phosphonoacetic acid sc in two injections. Phosphonoacetic acid-treated animals showed a reduction in the severity of disease. Neither serum viral antigen nor infectious virus could be detected. In phosphate buffered saline-treated animals both serum viral antigen and infectious virus were found. All animals treated with phosphate buffered saline died of myxomatosis. (Author abstract) (23 Refs)

60. INDUCTION OF EPSTEIN-BARR VIRUS EARLY ANTIGENS BY INTERCALATING CHEMICALS IN B95-8 CELLS.

Yamamoto N, Zur Hausen H
(c/o zur Hausen) Institut fur Virologie, Zentrum fur Hygiene der Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Virology; 115(2):390-394 1981

Various intercalating chemicals, such as ethidium bromide (ETB), proflavin (PF), acridine orange (AO), actinomycin D (AMD), methyl green (MG), Hoechst dye (HD), and trioxsalen (TX), have been tested for their effect on the induction of Epstein-Barr virus (EBV) antigens in several lymphoblastoid cell lines. ETB, PF, AO, and AMD enhanced induction of early antigens (EA) in B95-8 cells 3-to 10-fold. In contrast, viral capsid antigen (VCA) synthesis was not significantly affected by this treatment. Besides B95-8 cells only cells of the M-ABA line were induced to EA synthesis though to a lesser extent. All other cell lines tested did not respond to intercalating chemicals. Simultaneous treatment of B95-8 cells with ETB and 13-cis-retinoic acid inhibits the EA induction efficiently. ETB 'superinduced' EA neither in 12-O-tetradecanoyl-phorbol-12-acetate (TPA)- nor in iododeoxyuridine (IUdR)-treated B95-8 cells. (Author abstract) (29 Refs)

OTHER RELATED STUDIES

61. MONOCLONAL ANTIBODIES SPECIFYING TUMOR ASSOCIATED ANTIGENS AND THEIR POTENTIAL FOR DIAGNOSIS AND THERAPY (MEETING ABSTRACT).

Baldwin RW
Cancer Research Campaign Laboratories, University of Nottingham, Nottingham, NG7 2RD, England
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies specifying cell surface antigens on normal and malignant cells provide probes for investigating cell membrane changes in malignant transformation and for developing new approaches to cancer detection and treatment. Monoclonal antibodies directed against antigens associated with a naturally arising rat mammary carcinoma (Sp4) are produced by an interspecies hybridoma derived from a fusion of spleen cells from a syngeneic Sp4-immune rat with P3NS1 mouse myeloma cells. These antibody preparations (Sp4/A4) react specifically with tumor Sp4 cells when tested by membrane immunofluorescence or radioimmunoassays. The expression of Sp4 antigen on cells derived from tumors has also been demonstrated by analysis in the Fluorescence Activated Cell Sorter so providing a quantitative procedure for the analysis of cells derived from in vivo tumors. Sp4/A4 monoclonal antibody (rat IgG gamma 2b, mouse K chain) labelled with 125I specifically localizes in Sp4 tumor growing sc in syngeneic rats. Tumor localization was also demonstrated using 125I-labelled antibody by whole body gamma scintigraphy after 99mTc labelled blood pool subtraction. The therapeutic potential of conjugates of this antibody preparation conjugated to adriamycin have been evaluated. Adriamycin conjugated to antibody via a dextran bridge retained cytotoxic activity as assayed by an in vitro target cell survival. The conjugates also retained antibody activity binding to tumor Sp4 but not unrelated tumors. When tested in vivo the conjugates showed enhanced therapeutic effectiveness when tested against sc tumor grafts. (no Refs)

62. A SIGNIFICANT ROLE OF PROXIMITY OF HVJ-ANTIGEN IN THE GENERATION OF TUMOR IMMUNITY.

Kawashima K, Watanabe E, Kato Y, Suzuki H, Minami S, Isobe K, Ogura M, Nagura E, Yamada K
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan
Gan; 72(6):955-958 1981

According to the blocking test for proximity of cell surface antigens, L1210 leukemia-associated antigen was not linked to molecules carrying H-2d antigen or murine leukemia virus-associated antigen, but there was a close association between HVJ-associated antigen and L1210 leukemia-associated antigen on the surface membrane of HVJ-pi-infected L1210 leukemia cells. Once L1210 leukemia cells were infected with HVJ-pi, their adsorptive power was found to be greater than that of uninfected cells by quantitative absorption analysis. These phenomena may lead to a better recognition by the host of L1210 leukemia-associated antigen, followed by generation of tumor immunity. (Author abstract) (13 Refs)

63. HUMAN MALIGNANT GLIOMAS ASSOCIATED ANTIGENS (MEETING ABSTRACT).

de Muralt B, De Tribolet N, Diserens AC, Carrel S
Ludwig Institute for Cancer Research, 1066 Epalinges, Switzerland
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland . International Union Against Cancer 131 pp., 1981.

Hybridoma cells have been derived from a fusion between mouse myeloma cells P3X63 Ag/8 and spleen cells from a mouse immunized with whole cells of a human malignant glioma line LN-18. Three Hybrids were selected and cloned by limiting dilution. The specificity of the 3 monoclonal antibodies was investigated by an indirect antibody-binding radioimmunoassay on a panel of cell lines, short term cultures and fresh cell suspensions, derived from 37 human malignant gliomas, 3 meningiomas, 1 retinoblastoma, 1 medulloblastoma, normal fibroblasts and peripheral blood lymphocytes, as well as 18 cell lines from non gliogenous neoplasms. The monoclonal antibody GE2 bound to 17/18 gliomas cell lines, 16/17 short term glioma cultures and 1/2 fresh cell suspensions of gliomas. BF7 bound to 13/18, 15/17 and 1/2 respectively. They did not bind to any other cells and appear to react with common malignant glioma antigens. The third monoclonal antibody, C-G12, appears to react with a neural crest associated antigen since it was found to bind to 17/37 gliomas tested, 1 neuroblastoma, 1 medulloblastoma and 5/5 melanomas. Absorption with normal adult and fetal brain homogenate did not modify the binding

capacity of GE2 and BF7 but totally abolished the binding activity of C-G12. (no Refs)

64. IA-LIKE AND HLA-A,B ANTIGENS ON TUMOR CELLS IN LONG-TERM CULTURE.

Pellegrino MA, Weaver JF, Nelson-Rees WA, Ferrone S, Pious D, Alexander P, Uhr, Lennox ES, Dutton, Doherty PC, Martin WJ, Pollack MS
Dept. Pathology, Coll. Physicians and Surgeons, Columbia Univ., 630 West 168th St., New York, NY, 10032
Transplant Proc; 13(4):1935-1938 1981

Results of screening human tumor cells of nonlymphoid origin for expression of immune region-associated (Ia)-like antigens and human WBC antigen (HLA)-A,B allospecificities are summarized. Fifteen of the 29 tumor cell lines tested adsorbed the anti-Ia-like antigen MoAb Q5/13. Among the cell lines unable to adsorb MoAb Q5/13 were three Simian virus 40-transformed fibroblast lines. Testing of 48 cell lines for the ability to adsorb alloantisera to HLA-A1,A2, A3,A9,A10,B5,B7,B8,B12,B17 detected greater than 2 specificities at the A locus (A1,A2,A3) in the fetal lung line Hs1Lu and at the B locus (B5,B12, and B17) in the melanoma cell lines Hs 597T and Hs 695T and in the pagetoid sarcoma cell line Hs 925T. In every case, the extraspecificity could be explained by cross-reactivity in the HLA system. One breast carcinoma (Hs 578T) and one melanoma (Hs 695T) cell line tested at several passage levels displayed changes in adsorbing capacity for HLA-A,B alloantisera. Reactivity of cultured human tumor cells with HLA-A,B alloantisera was compared to that of autologous fibroblasts. Results indicate the following: expression of Ia-like antigens on t umor cells of nonlymphoid origin is not restricted to melanomas but may occur on other types of tumors, the HLA-A,B phenotype of tumor cells may change at different passage levels and may differ from that of autologous normal cells, but the changes mainly affect cross-reactivity patterns, and HLA typing may provide useful information to identify cross-species and intraspecies cell line contamination. (5 Refs)

65. ALIEN-DRIVEN DIVERSITY AND ALIEN-SELECTED ESCAPE: A RATIONALE FOR ALLOGENEIC CANCER IMMUNOTHERAPY.

Sondel PM, Hank JA
K4/430 Clinical Sciences Center, 600 Highland Ave., Madison, WI, 53792
Transplant Proc; 13(4):1915-1921 1981

We have presented two theories relating to the function of histocompatibility antigens and their presence as alien antigens on tumor cells. The theory of alien-driven diversity suggests that the ability to effectively recognize pathogens in the form of 'altered-self' derives from prior exposure to antigens cross-reactive with 'altered-self' during development. Furthermore, these cross-reactive antigens are alloantigens that are expressed on autologous cells during somatic development. These somatically generated alloantigens could be the result of the same genetic alterations that produced the polymorphism of these antigens within the species. Second, the theory of alien-selected escape suggest that a tumorigenic pathogen selects a cell bearing an alien H° antigen so that the alien-infected cell is recognized as self rather than altered-self by the tumor host. We then summarized data from mouse and man consistent with these theories and with the concept that clinically evident tumors have escaped the host's immune system. Finally, we have discussed potential directions for devising immunotherapy with allogeneic cells that might circumvent the apparent unresponsiveness of the patient's immune system to his own tumor. (Author abstract) (20 Refs)

66. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR ASSOCIATED ANTIGENS (MEETING ABSTRACT).

Starling JJ, Wright GL
Eastern Virginia Medical School, Norfolk, VA, 23501
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of spleen cells from Balb/C mice immunized against the prostate cancer cells line DU145, and the P3X63/Ag8 mouse myeloma line. The hybrids were screened for antibody production using glutaraldehyde-fixed or live cells in an in vitro binding radioimmunoassay (RIA). Antibody binding specificity was also checked by quantitative adsorption studies. A hybridoma clone (83.21) was isolated that secreted antibodies which preferentially bound to prostate and bladder cancer cells but did not bind to a variety of othe r normal and malignant human cell lines. This antibody also reacted with a cytomegalovirus-transformed human embryonic lung cell line but not to normal human embryonic lung cells. Conventional and competitive binding studies indicate that the 83.21 monoclonal antibody does not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, human WBC antigen (HLA), beta2 microglobulin, fibronectin, prostate specific antigen or DR antigens. Preliminary immunoprecipitation data with 125I-labeled, detergent soluble, DU145 membrane proteins and the 83.21 monoclonal antibody suggest that this antibody binds two proteins with mol wt of 210 and 97 kilodaltons. (no Refs)

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VIRAL IMMUNOLOGY

SERIES CB13 No. 82/06

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. HEPATITIS B ANTIGEN IN THE LIVER IN HEPATOCELLULAR CARCINOMA IN SHIKOKU, JAPAN.

Akagi G, Furuya K, Otsuka H
2nd Dept. Pathology, Sch. Medicine, Kuramoto-cho 3-18-15, Tokushima 770, Japan
Cancer; 49(4):678-682 1982

An analysis of 105 autopsy cases (77 male, 28 female) of hepatocellular carcinoma (HCC) showed that 90 cases (85.7%) were associated with liver cirrhosis, of which 75 cases (83.3%) were of the macronodular type. Hepatitis B surface antigen (HBsAg) was detected with orcein stain in the hepatic tissue in

HE 20.3172/2:

58 cases (55.2%). The incidence of HBsAg in cases of HCC patients with cirrhosis (58.9%) was higher, but not significantly, than that in those without cirrhosis (33.3%). The mean age of HBsAg-positive cases was 5 yr less than that of HBsAg-negative cases, the age distributions therefore being significantly differ ent. (Author abstract) (43 Refs)

2. UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA IN ADOLESCENT AND YOUNG ADULTS. REPORT OF 4 CASES TREATED BY RADIOTHERAPY AND CHEMOTHERAPY (MEETING ABSTRACT).

Boilletot A, Stierle JL, Pillement P, Bergerat JP, Bernard C, Lang JM, Oberling F
Hopital de Hautepierre, Strasbourg, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Four patients, 10 to 23 yr old, were treated for malignant undifferentiated nasopharyngeal carcinoma (UNC) between October 1978 and September 1980 by radiotherapy and BACOP chemotherapy (bleomycin, adriamycin, cyclophosphamide, vincristine, predinosone). One patient was Magrebian and 3 were Caucasian. Most patients presented clinical features a long time before diagnosis (3 to 10 mo), such as chronic catarrhal otitis (2 pts), headache (1 pts), cervical adenomegaly (1 pt). In all cases, cavum was the primary tumor site. Three patients had malignant involvement of the sphenoidal bone. Among them, two developed metastasis later (lung and dorsal spine). Epstein-Barr virus (EBV) serial serological studies showed elevated antibody titers against VCA (viral capsid antigen), early antigens, Epstein-Barr virus associated nuclear antigens (EBNA) at the time of diagnosis, which decreased slowly during the treatment. However anti-VCA antibody titer increased regularly in one patient despite adequate radiotherapy of primary site, and a bone metastasis was discovered 15 days later. HLA typing showed A2 haplotype in one patient, B7 haplotype in 2 patients, and a deletion of both B loci in a 3rd one. All patients were treated by local radiotherapy up to 50 to 70 Gray (Gy) on the primary site and 50 Gy on cervical lymphnodes. BACOP chemotherapy in 5-day courses was given in all patients. Two non metastatic patients received BACOP chemotherapy because of slow tumor regression. The 2 other patients received 6 courses BACOP chemotherapy after they developed metastasis and were irradiated up to 50 Gy on the metastatic site. They all went into complete remission. Total survival duration is 9+ to 33+ mo. BACOP chemotherapy seems to be a valuable chemotherapy in metastatic malignant UNC. Thus its use as adjuvant treatment in non metatatic disease has to be discussed. (no Refs)

3. VULVAR INTRAEPITHELIAL NEOPLASIA: CORRELATION OF NUCLEAR DNA CONTENT AND THE PRESENCE OF A HUMAN PAPILLOMA VIRUS (HPV) STRUCTURAL ANTIGEN.

Crum CP, Braun LA, Shah KV, Fu YS, Levine RU, Fenoglio CM, Richart RM, Townsend DE
Div. Ob/Gyn Pathology, Columbia Univ. Coll. of Physicians and Surgeons, 630 West 168th St., New York, NY, 10032
Cancer; 49(3):468-471 1982

Immunoperoxidase localization of a human papilloma virus structural antigen (HPV) was attempted in 68 intraepithelial lesions of the vulva, 39 of which were analyzed for nuclear DNA content by microspectrophotometry. Overall, 5.9% (4/68) stained positive for HPV. Ninety per cent (35/39) of the cases tested were aneuploid, and, of these, 2.8% (1/35) stained positive for HPV. In contrast, 50% (2/4) of the polyploid lesions were positive. Hence DNA microspectrophotometry and immunoperoxidase localization of HPV are useful coparameters for distinguishing wart virus infection (condylomata) from vulvar intraepithelial neoplasia. HPV is detected infrequently within aneuploid lesions, in keeping with the concept that epithelial maturation is required for virion assembly. Whether the HPV genome exists in a nonreplicative state within the aneuploid cell population is unknown. (Author abstract) (18 Refs)

4. THE RIDDLE OF HODGKIN CELLS.

Diehl V
Abt. Hamalotogie, Medizinische Hochschule Hannover, Hannover, W. Germany
MMW; 123(48):1827-1828 1981

Characteristics of the first tumor cell cultures successfully established from biopsy material of patients with Hodgkin's disease are described. Testing for markers of differentiation revealed that the cell lines had antigenic properties similar to those of early myelo-monocytes. Although the cell lines were established from biopsy specimens of four patients, they possessed many identical characteristics, identical marker chromosomes, and common cytochemical features. One of the four cell lines was positive for an Epstein-Barr-virus (EBV)-induced antigen, and another cell line possessed EBV receptors. The cell lines were poor inducers of tumor growth in nude mice. (no Refs) (In GER)

5. EARLY ORAL SIGNS OF BURKITT'S LYMPHOMA CELL LEUKEMIA.

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J Oral Med; 36(4):107-110 1981

Burkitt's lymphoma cell leukemia in two patients (females, 12.5 and 15 yr old) with early appearance of oral signs is reported. The younger patient had gingival swelling, mobility of teeth, sensitivity to percussion, and submandibular lymph nodes that were palpable and sensitive. The oral mucosa was intact. No evidence of dental disease proper was found. Radiological examination showed bone resorption with loss of crest in the area of the lower right first and second molars. Laboratory tests a few days after hospitalization showed leukocytosis (16,700 WBC/ml(3)). Bone marrow was heavily infiltrated by Burkitt's cells that carried B-cell markers but lacked Epstein-Barr virus nuclear antigen (EBNA), viral capsid antigen (VCA), and early antigen (EA). Disease progression was rapid, in spite of aggressive chemotherapy; the patient died after 6 mo. The older patient showed similar signs with spontaneous bleeding and pain in the gum s and complete bilateral loss of sensation in the lower lip and chin. The maxilla and mandible were equally involved. Aggressive chemotherapy produced initial remission, but the patient relapsed twice with meningeal leukemia. The patient died of tumor despite cranial irradiation and cytotoxic therapy. Both cases were unusual in the early appearance of oral signs, which most commonly develop in later stages. Findings suggest conversion of Burkitt's lymphoma to leukemia. (21 Refs)

6. SISTER-CHROMATID EXCHANGE IN PATIENTS WITH HEPATITIS.

Ghosh PK
Dept. Anthropology, Univ. Delhi, Delhi-110 007, India
Mutat Res; 103(3-6):303-306 1982

The lymphocytes of 28 adult patients, 12 of whom had virus 'A' and 16 of whom had virus 'B' hepatitis as determined by serum antigen tests, were examined for sister-chromatid exchanges (SCEs) induced by bromodeoxyuridine (10 ug/ml). Patients with virus 'A' hepatitis had a mean SCE/cell of 8.61 +-2.21, those with virus 'B' had a mean SCE/cell of 10.12 +-2.83; 20 control patients' lymphocytes averaged 5.21 +-1.26 SCE/cell. After complete chemical and biochemical recovery, 2/6 of the virus 'A' hepatitis patients and 1/5 of the virus 'B' hepatitis patients had reduced SCEs, although not to levels equivalent to controls. Failure of SCE levels to return to control levels may have been due to the presence of the not replaced virally-affected lymphocytes still in the system after the patients had recovered. (17 Refs)

7. CHARACTERISTICS OF A BRAIN LYMPHOMA CELL LINE DERIVED FROM PRIMARY INTRACRANIAL LYMPHOMA.

Miyoshi I, Kubonishi I, Yoshimoto S, Hikita T, Dabasaki H, Tanaka T, Kimura I, Tabuchi K, Nishimoto A
Dept. Medicine, Kochi Medical Sch., Kochi 781-51, Japan
Cancer; 49(3):456-459 1982

A brain lymphoma cell line, designated TK, was established from biopsy material of a patient with primary intracranial lymphoma. The TK cell line grew in suspension with clumps of cells and consisted of primitive lymphoid cells. TK cells and original lymphoma cells from which the cell line was derived bore surface immunoglobulin and lacked Epstein-Barr virus-determined nuclear antigen. Transplantation of the TK cells into immunosuppressed newborn hamsters gave rise to invasive growth of tumors with metastasis to the brain and eyes. These findings provide evidence for a B-cell origin of the brain lymphoma in this case. (Author abstract) (13 Refs)

8. HISTOLOGICAL TYPES OF NASOPHARYNGEAL CARCINOMA AS COMPARED TO EBV SEROLOGY.

Krueger GR, Kottaridis SD, Wolf H, Ablashi DV, Sesterhenn K, Bertram G
Immunopathology Labs., Univ. Cologne, Joseph-Stelzmann-Strasse 9, 5000 Koln 41, W. Germany
Anticancer Res; 1(4):187-194 1981

One hundred and thirteen cases of nasopharyngeal carcinoma were classified according to the World Health Organization (WHO)-, French-, and Cologne classification systems and the various histologically defined types were correlated with data on Epstein-Barr virus (EBV) serology (EA, VCA, EBNA, CF, and IgA-VCA). Significantly elevated titers of anti-EBV antibodies were found primarily in undifferentiated carcinomas with or without lymphoid infiltration and in non-keratinizing carcinomas (NKC) with lymphocytic infiltration. The classification systems used, when combined with clinical data, correlated well with results of serological investigations for EBV induced antibodies, and may help identify the primary tumor site. Of the three systems studied, the French system was the simplest and correlated well with serologic data. An undifferentiated carcinoma of the 'nasopharyngeal type' could be misdiagnosed if serologic studies were not performed. The WHO classification had limited reproducibility for differentiating NKC from undifferentiated carcinomas. NKC were heterogeneous with respect to their EBV related pathogenesis. The Cologne modification of the WHO system may eliminate some of these problems of the WHO system. It is recommended that any of the two proposed classification systems be used in parallel and together with adequate serological studies. (29 Refs)

9. NASOPHARYNGEAL CARCINOMA IN AMERICAN CHILDREN: EPSTEIN-BARR VIRUS-SPECIFIC ANTIBODY TITERS AND PROGNOSIS.

Naegele RF, Champion J, Murphy S, Henle G, Henle W
Div. Infectious Diseases, St. Jude Children's Res. Hosp., Memphis, TN
Int J Cancer; 29(2):209-212 1982

Seven American juvenile patients with undifferentiated or nonkeratinizing nasopharyngeal carcinoma (NPC) were examined serially for Epstein-Barr virus (EBV)-specific antibody spectra and titers in sera. At diagnosis, all showed antibody patterns characteristic of NPC: ie, high titers of IgG antibodies to viral capsid antigen (VCA) and to the diffuse (D) component of the early antigen complex. Six patients had IgA antibodies to VCA, and four to the D component. In the patients who responded to therapy with complete and maintained remissions, the IgG antibodies to D and the IgA antibodies to VCA and D decreased to undetectable levels within 12 to 30 mo. By contrast, of the four patients who responded only transiently to therapy, three showed substantial increases and one continuously high titers of IgG anti-D and IgA anti-VCA. The increases in antibody titers preceded clinical recognition of recurrent tumors by 1 to 6 mo. Three of these patients have died and the fourth is alive with disease. These data indicate that American juvenile NPC does not differ from the adult disease observed anywhere in the world. They reaffirm the potential usefulness of EBV-specific serology in the diagnosis and prognosis of NPC and the monitoring of patients following therapy. (Author abstract) (35 Refs)

10. THE EFFECT OF CHRONIC HABITUAL ALCOHOL INTAKE ON THE DEVELOPMENT OF LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: RELATION TO HEPATITIS B SURFACE ANTIGEN CARRIAGE.

Ohnishi K, Iida S, Iwama S, Goto N, Nomura F, Takashi M, Mishima A, Kono K, Kimura K, Musha H, Kotota K, Okuda K
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Cancer; 49(4):672-677 1982

To study the effects of habitual alcohol intake on the latency period for the development of liver cirrhosis and hepatocellular carcinoma (HCC), 158 patients with cirrhosis and 79 with HCC were analyzed with respect to age at the time of diagnosis. They were classified into four groups based on hepatitis B surface antigen (HBsAg) in serum, and the history of intake of more than one small bottle of Japanese 'sake' or an equivalent per day for more than 10 yr. The av age of HBsAg positive male cirrhotics with a drinking habit (n = 10) was 38.8 yr, 10.5 yr younger than that of those without a drinking habit (n = 8) (p less than 0.05). The av age of HBsAg negative cirrhotics with a drinking habit (n = 97) was 47.9 yr, 8 yr younger than that of those not drinking (n = 36) (p less than 0.001). There was no significant difference in the laboratory data between these groups. The av age of the HBsAg positive HCC patients with a drinking habit (n = 20) was 48.9 yr, 9 yr younger than that of those without a drinking habit (n = 12) (p less than 0.05). The av age of HBsAg negative male HCC cases with habitual intake of more than 126 ml of ethanol per day

was 51.0 yr (n = 8), 10 yr younger than that of nondrinking male HCC cases (n = 11) (p less than 0.05). These data suggest that habitual alcohol intake may promote the development of liver cirrhosis and HCC, especially in HBsAg carriers. (Author abstract) (29 Refs)

11. MEMBRANOUS OBSTRUCTION OF THE INFERIOR VENA CAVA: ETIOLOGY AND RELATION TO HEPATOCELLULAR CARCINOMA.

Okuda K
Dept. Medicine, Chiba Univ. Sch. Medicine, Chiba, Japan
Gastroenterology; 82(2):376-379 1982

Membranous obstruction of the inferior vena cava (MOVC) and relations to hepatocellular carcinoma (HCC) are reviewed. MOVC appears to occur more frequently in developing areas of the world. The relationship between MOVC and (HCC) is poorly understood and may represent multifactorial oncogenetic processes. In a recently reported series, incidence of 22.2% hepatitis B surface antigen (HBsAg) in patients with MOVC in South Africa was higher than in healthy persons (8.7%), but lower than that in patients with HCC (33.7%). This may suggest that hepatitis B virus infection is not the only factor in hepatocarcinogenesis, and that high incidence of HCC patients with MOVC may be due to the long duration of chronic liver damage in MOVC. HCC has been described also with a wide variety of chronic liver diseases including hemochrom atosis, alpha1-antitrypsin deficiency, schistosomiasis, clonorchiasis, and Thorotrast liver disease. Since the incidence of HBsAg carrier state is much higher in blacks of South Africa, but the incidence of HCC is similar to that of Japan, perhaps blacks are exposed to lower concentrations of chemical carcinogens. (30 Refs)

12. HEPATOCELLULAR CARCINOMA ARISING IN NONCIRRHOTIC AND HIGHLY CIRRHOTIC LIVERS: A COMPARATIVE STUDY OF HISTOPATHOLOGY AND FREQUENCY OF HEPATITIS B MARKERS.

Okuda K, Nakashima T, Sakamoto K, Ikari T, Hidaka H, Kubo Y, Sakuma K, Motoike Y, Okuda H, Obata H
Dept. Medicine, Chiba Univ. Hosp., Chiba, Japan
Cancer; 49(3):450-455 1982

Hepatocellular carcinoma (HCC) associated with cirrhosis and HCC developing in a noncirrhotic liver may have differing pathogeneses. To study this possibility, 426 autopsied cases of HCC were investigated. Of these, 45 livers were not cirrhotic, 50 were highly cirrhotic (liver wt less than 99 g), and the remaining 331 were cirrhotic but not so highly. The av age was significantly older in the highly cirrhotic group, suggesting a longer premalignant period of chronic liver disease. The liver wt in the noncirrhotic group was about 3.5 times that in the highly cirrhotic group. Hepatitis B surface antigen was positive in serum in only 9.3% and in liver tissue in 10% in the noncirrhotic cases, the positivity rate being much lower compared with other groups (p less than 0.005-0.01), yet antibody to HB core was positive in 90%. The antibody titers were low, however, indicating that these noncirrhotic patients had in the past had HB virus (HBV) infection with no residual chronic B hepatitis. Analysis of the grades of anaplasia of cancer tissue demonstrated an inverse correlation between the degree of fibrosis and grade of anaplasia, i.e., the more advanced the fibrosis, the less anaplastic the cancer. These data suggest that HCC arising in highly cirrhotic livers and in noncirrhotic livers have different pathogenetic backgrounds, and that HBV infection, even though transient, has a certain role in hepatocarcinogenesis. The generally held conjecture that HCC in a noncirrhotic liver is caused by nonviral carcinogens and HCC arising on the ground of cirrhosis is due to HBV seems untenable in such a simple concept. (Author abstract) (27 Refs)

13. CORRELATION BETWEEN MIXED LYMPHOCYTE CULTURES AND ANTI-EPSTEIN BARR VIRUS (EBV) ANTIBODIES IN HODGKIN'S DISEASE AND NON HODGKIN LYMPHOMA PATIENTS.

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Biomedicine [Express]; 35(5):153-156 1981

Cellular and humoral immunity was examined in Hodgkin's disease and non Hodgkin lymphoma (33) patients and compared with a normal group. Mixed lymphocyte cultures (MLC) were used as a par ameter for cell mediated immunity and anti-Epstein Barr virus (EBV) antibodies for specific humoral immunity. High stimulation indices coincided with low anti-VCA and anti-EBNA titers in the control group (r =-0.343). This negative correlation was not found in non Hodgkin lymphomas and was substantially lower (r =-0.142) in Hodgkin's disease. The alterations in immunoregulatory mechanisms in these patients are discussed. (Author abstract) (29 Refs)

14. SELECTING BINDING AND COMPLEMENT-MEDIATED LYSIS OF HUMAN HEPATOMA CELLS (PLC/PRF/5) IN CULTURE BY MONOCLONAL ANTIBODIES TO HEPATITIS B SURFACE ANTIGEN.

Shouval D, Wands JR, Zurawski VR, Isselbacher KJ, Shafritz DA
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Proc Natl Acad Sci USA; 79(2):650-654 1982

High-affinity 125I-labeled monoclonal antibodies to hepatitis B virus surface antigen (HBsAg) bind to a human hepatocellular carcinoma cell line, PLC/PRF/5, which synthesizes and secretes HBsAg. These monoclonal antibodies of the IgG1, IgG2a, and IgM isotypes are directed against different antigenic determinants on HBsAg and, in the presence of complement, both anti-HBs IgG2a and IgM, but not anti-HBs IgG1, lyse PLC/PFR/5 cells in culture. Although there is a low level of anti-HBs binding (especially with anti-HBs IgM) to human hepatoma cell lines which do not synthesize HBsAg (SK-Hep 1 and Mahlavu cells), this interaction does not lead to complement-mediated cell lysis and is thought to be nonspecific. Minimal binding of 125I-labeled anti-influenza HA antigen IgM binding to PLC/PRF/5 cells was also detected, but this likewise did not lead to complement-mediated cell lysis. These results indicate that a human hepatocellular carcinoma cell line, persistently infected with hepatitis B virus, can be recognized and lysed by monoclonal antibodies directed against specific determinants of HBsAg. Monoclonal antibodies to this viral envelope protein may prove to be useful immunodiagnostic and immunotherapeutic agents when such viral epitopes are expressed on the surface of infected cells. (Author abstract) (33 Refs)

15. THE RELATIONSHIP OF HEPATITIS B ANTIGENS TO HEPATOCELLULAR CARCINOMA AND LIVER CIRRHOSIS - A CYTOCHEMICAL EXAMINATION OF LIVER OF 462 CASES.

Yan R, Gan L, Huang G
Dept. Cancer Res., Guangxi Medical Coll., Guangxi Province, People's Republic of China
Zhonghua Zhongliu Zazhi; 3(2):143 1981

Using Shikata's and Gomori's staining methods, hepatitis B surface antigens (HBSAG) were analyzed in 462 liver specimens from various sources in order to study the relationship between hepatitis B, liver cirrhosis and hepatoma. Among the hepatoma patients (192 cases), 71.8% were complicated with liver cirrhosis, with an HBSAG-positive rate of up to 76.5%. It was concluded that the occurrence of hepa toma is closely related to HBSAG, especially when it is present in liver cirrhosis. (no Refs) (In CHI)

16. ANTICOMPLEMENT IMMUNOENZYMATIC METHOD OF DETECTING EPSTEIN-BARR NUCLEAR ANTIGEN IN NASOPHARYNGEAL CARCINOMA CELLS IN NORMAL EPITHELIAL CELLS.

Zeng Y, Shen S, Pi G, Ma J, Zhang Q, Zhao M, Dong H
Inst. Virology, Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Chin Med J [Engl]; 94(10):663-668 1981

Epstein-Barr nuclear antigen (EBNA) was tested for by both anticomplement immunofluorescence and anticomplement immunoenzymatic (ACIE) methods in nasopharyngeal cells from 79 patients with nasopharyngeal carcinoma (NPC), cells from 66 patients with suspected NPC, cells from head and neck tumors other than NPC (18), and cells from the nasopharyngeal mucosa of 3-8 mo old dead fetuses (21). ACIE studies of exfoliated cells indicated NPC in 79 cases, of which 62 were also NPC-positive upon histologic and cytologic examination, 10 were NPC-positive by histologic examination only, and 7 were NPC-positive by cytologic examination only. Nine of the suspected cases were NPC-positive by the ACIE method, but were negative upon cytologic or histologic examination. None of the head neck tumor smears or fetal mucosa cells were NPC-positive by any method used. The findings of EBNA in carcinoma cells, hyperplastic epithelial (HE) cells, and ciliated columnar epithelial (CCE) cells of NPC patients, and in HE cells and CCE cells of normal individuals, but with less found in squamous epithelial cells, suggest that Epstein-Barr virus infects normal epithelial cells first, especially CCE cells, integrating its DNA into cellular DNA. (11 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

17. A 53-KILODALTON PROTEIN COMMON TO CHEMICALLY AND VIRALLY TRANSFORMED CELLS SHOWS EXTENSIVE SEQUENCE SIMILARITIES BETWEEN SPECIES.

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Proc Natl Acad Sci USA; 79(2):287-291 1982

A heat-stable DNA-binding protein with subunits of about 53 kilodaltons (kDal) was purified from two virally transformed human cell lines (Epstein-Barr virus-positive Raji and Namalwa) and two mouse tumor cell lines (methylcholanthrene-induced Meth A sarcoma and TA3 mammary carcinoma). All four 53-kDal proteins showed closely related total amino acid compositions, similar peptide maps, and identical NH2-terminal amino acid sequences for 20 residues. These 53-kDal proteins are therefore evolutionarily highly conserved, independent of whether they originate from virally or chemically transformed cells. The NH2-terminal sequence and the protein chain as a whole are not hydrophobic; however, some unexpected residue distributions were observed. Comparisons with other proteins reveal no clear sequence similarity with known tumor antigen structures, homologous immunoglobulins, or some other proteins of known sequence. Epstein-Barr virus-determined nuclear antigen also appears to have a different NH2-terminal sequence. Thus, the results show that the 53-kDal proteins represent a unique protein type with little species variation; this finding suggests that these proteins must perform an important common function in different transformation systems. (Author abstract) (38 Refs)

18. GASTRIN AND THE TRANSFORMING PROTEIN OF POLYOMA VIRUS HAVE EVOLVED FROM A COMMON ANCESTOR.

Baldwin GS
Melbourne Tumour Biology Unit, Melbourne, Australia
FEBS Lett; 137(1):1-5 1982

While gastrin and the transforming protein (middle T antigen) of polyoma virus appear to be superficially dissimilar molecules, a hitherto unreported structural relationship between the two proteins is presented, which supports the hypothesis that they have evolved from a common ancestor. (54 Refs)

19. INDUCTION OF EPSTEIN-BARR VIRUS NUCLEAR ANTIGEN AND DNA SYNTHESIS IN A HUMAN EPITHELIAL CELL LINE AFTER EPSTEIN-BARR VIRUS INFECTION.

Ben-Bassat H, Mitrani-Rosenbaum S, Goldblum N
Dept. Hematology, Hadassah Univ. Hosp., Jerusalem, Israel
J Virol; 41(2):703-708 1982

The association of Epstein-Barr virus (EBV) with nasopharyngeal carcinoma is supported by the presence of EBV genomes in the epithelial elements of the tumor and by elevated antibody titers to EBV-specific antigens in the patients; the levels of these titers are related to the clinical course of the disease. However, since most laboratory data suggest that EBV is a B-lymphotropic virus, it is unclear how the virus becomes associated with the epithelial elements of the nasopharynx. The purpose of the present work was to find a human model system to study this association. A human epithelial line (U) was found that could be directly infected by EBV, and viral functions, the induction of EBV nuclear antigen and cellular DNA synthesis, were demonstrated. The U line was established in 1957 by the late H J Van Kooten (Kok-Doorschodt at the University of Utrecht), and although it is no longer diploid, it exhibits density inhibition. When U cells were infected with EBV, EBV nuclear antigen was expressed in 6 to 16% of the cells, 1 and 2 days after infection with B95-8 virus, but not with the P3HR-1 strain. No evidence for virus replication was obtained; immunofluorescence staining for early antigens and virus capsid antigens gave negative results. Quantitative adsorption experiments for EBV indicated that the adsorption capacity of U cells is significant (60% of Raji cells). The present results also demonstrated that infection with the virus overcomes block(s) in cellular DNA synthesis caused by 5-fluoro-

deoxyuridine. The induction of DNA synthesis was determined by increased incorporation of [3H]thymidine into the cells. The highest level of isotope incorporation was observed at about 15 hr after infection and thereafter decreased. Analysis of the induced DNA indicated that it was of cellular origin. (Author abstract) (36 Refs)

20. TERRITORIAL LIMITS AND FUNCTIONAL ANATOMY OF THE SIMIAN VIRUS 40 REPLICATION ORIGIN.

Bergsma DJ, Olive DM, Hartzell SW, Subramanian KN
Dept. Microbiology and Immunology, Univ. Illinois Medical Center, Chicago, IL, 60612
Proc Natl Acad Sci USA; 79(2):381-385 1982

The region at and near the simian virus 40 (SV40) DNA replication origin contains a series of palindromes, a 17-base pair (bp) A+T-rich sequence, three copies of a 21-bp repeat, and two copies of a 72-bp repeat. We have constructed a series of recombinant plasmids containing sequential deletions at the region of SV40 DNA replication origin starting from the end near the repeats. These deletions were introduced by using in vitro and in vivo techniques. The relative replication efficiency of these recombinant plasmids were directly assayed in COS-1 monkey kidney cells capable of providing the tumor antigen necessary for the replication of these molecules. Recombinants lacking both copies of the 72-bp repeat did not exhibit any reduction in replication efficiency. Recombinants lacking the 21-bp repeats showed decreased replication efficiency; the reduction in replication efficiency was proportional to the number of copies of the 21-bp repeat deleted in these recombinants. A recombinant retaining the palindromes at the region of origin of SV40 DNA replication but lacking the A+T-rich sequence and the repeats failed to replicate. Based on these results, the SV40 DNA replication origin is subdivided into two regions, and their boundaries are defined. One of these two regions, and their boundaries are defined. One of these two regions is a core region containing the 17-bp, 15-bp, and 27-bp palindromes and, quite likely, the 17-bp A+T-rich sequence which are necessary for replication. The other is an auxiliary region that consists of the 21-bp repeats and has a dose-dependent enhancement effect on replication efficiency. (Author abstract) (34 Refs)

21. RELATIONSHIP OF OLIGOMERIZATION TO ENZYMATIC AND DNA-BINDING PROPERTIES OF THE SV40 LARGE T ANTIGEN.

Bradley MK, Griffin JD, Livingston DM
Sidney Farber Cancer Inst., Boston, MA, 02115
Cell; 28(1):125-134 1982

Crude and highly purified SV40 large T antigen has been found to exist in forms of various sizes. Immunoreactive structures of 5.5S (80-85 kd), 7S (approx 150 kd) and 15.5S (325-340 kd) have been identified by zonal sedimentation and gel filtration. They appear to correspond to monomeric, dimeric and tetrameric species of T, respectively, and are free of detectable 55 kd NVT by specific immunoprecipitation analyses. While highly purified monomer appears relatively inactive in SV40 DNA-binding and ATPase asays, both the dimer and tetramer display these activities. By contrast, all three comigrate with casein kinase activity. These data suggest that the protein can exist as a monomer and in various homoaggregated forms. In addition, it appears that it must aggregate to be an active DNA-binding element and an ATPase. (Author abstract) (46 Refs)

22. BIOLOGY OF SIMIAN VIRUS 40 (SV40) TRANSPLANTATION ANTIGEN (TRAG). VIII. RETENTION OF SV40 TRAG SITES ON PURIFIED SV40 LARGE T ANTIGEN FOLLOWING DENATURATION WITH SODIUM DODECYL SULFATE.

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Virology; 117(1):267-270 1982

Simian virus 40 (SV40) large tumor (T) antigen was isolated from SV40-infected permissive and -transformed cells by immunoprecipitation with anti-T sera and purified by electrophoresis on solubilizable SDS-polyacrylamide gels. This method proved to be a rapid and efficient procedure for purifying T antigen as 74% of the immunoprecipitated T antigen was subsequently recovered. The purified, SDS-denatured large T antigen retained its ability to react with anti-T antibody and to immunize mice against a challenge of syngeneic SV40 tumor cells, indicating that the antigenic sites present on the large T antigen molecule that induce a tumor rejection response in vivo are resistant to denaturation by SDS. (Author abstract) (25 Refs)

23. REGULATION OF SV40 GENE EXPRESSION.

Graessmann A, Graessmann M, Mueller C
Institut fur Molekularbiologie und Biochemie, Freien Universitat Berlin, Berlin, W. Germany
Adv Cancer Res; 35:111-149 1981

The microinjection approach to the study of simian virus 40 (SV40) and polyoma virus (PV) gene expression is discussed. The technique permits placing of biological material from virtually any source directly into living, single-tissue culture cells using glass micropipettes. Cell type dependence of SV40 and PV gene expression is presented in relation to permissive, nonpermissive, semi-permissive, and virus-resistant cells. Functions of SV40 tumor antigens are considered, including induction of cellular and viral DNA systems, regulation of late and early SV40 gene expression, stimulation of rRNA synthesis, helper function for adenovirus and U antigenicity, and reduction of the actin cable structure. Experiments with microinjection of SV40 DNA fragments to induce cellular transformation and applications of microinjection are reviewed. (78 Refs)

24. CELL SURFACE BINDING AFFINITY OF SIMIAN VIRUS 40 T-ANTIGEN.

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Virology; 117(1):173-185 1982

Simian virus 40-transformed cells are characterized by a virus-induced tumor transplantation antigen (SV40 TSTA) defined in vivo by the rejection of tumorigenic SV40-transformed cells in SV40-immunized mice and in vitro by SV40 tumor cell-specific cytotoxic T cells. Several experimental findings support the notion that SV40-infected and -transformed cells express SV40 large tumor antigen (T-Ag) or closely related antigens on the cell surface (surface T). In this report, evidence is presented for a cell surface binding affinity of SV40 T-Ag solubilized and extracted by disruption of SV40-transformed and SV40-infected cells in growth medium. Incubation of various transformed and nontransformed living monolayer cells in situ with these extracts led to a significant uptake of T-Ag to the cell surface (called 'externally bound T-Ag') up to 2-5x higher amounts in comparison to native surface T on SV40-

transformed cells. This was demonstrated by the highly sensitive 125I-protein A assay using rabbit antisera directed against purified SV40 T-Ag. Serological analysis of T-Ag in cellular extracts and of externally bound T-Ag revealed no apparent differences suggesting the cell surface binding affinity as a new property of SV40 T-Ag. We interpret our results as an indication that this property enables purified T-Ag to initiate the cellular immune response necessary for the SV40-tumor rejection in mice. (Author abstract) (40 Refs)

25. SPECIFIC INTERACTION OF THE SV40 T ANTIGEN-CELLULAR P53 PROTEIN COMPLEX WITH SV40 DNA.

Reich NC, Levine AJ
(c/o Levine) Dept. Microbiology, State Univ. New York Stony Brook, Sch. Medicine, Stony Brook, NY, 11794
Virology; 117(1):286-290 1982

Three forms of the simian virus 40 (SV40) large tumor antigen (T antigen), free T antigen from infected monkey cells, T antigen-p53 complex from virus-infected mouse cells, and T antigen-p53 complex from SV40-transformed mouse cells, were examined for their abilities to bind specifically to SV40 DNA. Employing an immunoassay that detected T antigen and/or p53 protein bound to restriction fragments of viral DNA, it was shown that all three of these forms of SV40 T antigen bind preferentially to the restriction fragment of SV40 DNA containing the nucleotide sequence at the origin of viral DNA replication. Free p53 protein alone failed to bind to SV40 DNA in this assay. These results indicate that the SV40 T antigen-p53 protein complex displays the same SV40 DNA binding specificity as free T antigen obtained from a productive infection. (Author abstract) (24 Refs)

26. INITIATION AND REGULATION OF SIMIAN VIRUS 40 EARLY TRANSCRIPTION IN VITRO.

Lebowitz P, Ghosh PK
Dept. Internal Medicine, Yale Medical Sch., New Haven, CT, 06510
J Virol; 41(2):449-461 1982

We have studied initiation and regulation of early transcription of simian virus (SV40) DNA in vitro by eucaryotic RNA polymerase II, using both a crude HeLa cell extract and a partially purified calf thymus polymerase supplemented with a HeLa cell S100 fraction. Analysis of initiation sites by primer-directed cDNA synthesis and sequencing of cDNA's has revealed that early transcription is initiated at a multiplicity of sites corresponding to the 5' termini of early viral mRNA's. The pattern of in vitro initiation closely resembles the pattern of 5' termini of early mRNA's late in the lytic cycle, with principal initiations between residues 5184 to 5194, upstream from the early Hogness-Goldberg (TATA) sequence, and at residue 5123, well downstream from this sequence. In vitro transcription is initiated to a lesser extent at sites between residues 5150 and 5155, the principal 5' termini of early mRNA's in transformed cells and early in lytic infection, located 21 to 26 nucleotides downstream from the TATA sequence. Initiation occurs at identical sites and with similar efficiencies on form I and linearized DNA templates. There are minor differences in the efficiency of initiation at specific sites by the two transcriptional systems. Studies using a DNA template cleaved just downstream from the TATA sequence and a second template cleaved through a pair of 72-base-pair tandem repeats starting 87 nucleotides upstream from the TATA sequence have revealed that neither the TATA sequence nor the repeats are essential for early transcription in vitro. However, removal of the TATA and upstream sequences shifts initiation of transcription principally to the residue 5123 site. Comparison of the relative efficiencies of transcription on intact wild-type DNA, the two cleaved DNAs, and DNA from a deletion mutant suggests that all or most of the sequences constituting an early promoter lie within the genomic region 60-70 to 140 nucleotides upstream from the principal 5' termini of the early mRNA's. (Author abstract) (43 Refs)

27. ESTABLISHMENT OF MACROPHAGE-LIKE CELL LINES OF THE GUINEA PIG.

Kato K, Katoaka T, Ohnuki T, Tokunaga T
Dept. Enteroviruses, Natl. Inst. Health, Kamiosaki, Shinagawa-ku, Tokyo, Japan
Microbiol Immunol; 25(11):1209-1214 1981

The establishment of three macrophage-like cell lines from adherent cells of peritoneum and bone marrow of strain 13 guinea pigs infected with SV40 and BK viruses is reported. These lines are adherent, phagocytic and secrete lysozyme. Two express guinea pig leukocyte antigens while one does not. (17 Refs)

28. NEW EPSTEIN-BARR VIRUS VARIANTS FROM CELLULAR SUBCLONES OF P3J-HR-1 BURKITT LYMPHOMA.

Heston L, Rabson M, Brown N, Miller G
(c/o Miller) Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Nature; 295(5845):160-163 1982

Correlation between biological properties and genome structure was examined in 2 9 subclones of HR-1 virus, an Epstein-Barr virus (EBV) mutant that does not immortalize lymphocytes or induce lymphomas. None of the 29 clones spontaneously released EBV DNA in an amount comparable to that of the parental line. Differences in viral DNA content correlated with lower levels of viral capsid antigen (VCA) clones. Enhanced VCA expression occurred in five clones that released large amounts of DNA after treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). The subclonal viruses resembled HR-1 in lack of immortalization, cytotoxicity, and interference with transformation; unlike HR-1, they did not induce virus early antigen (EA) synthesis in Raji cells. Differences in the DNAs of nontransforming virus (HR-1 and its subclones) and two transforming EBV strains were found to involve at least six regions of the genome. HR-1 DNA differed from the DNA of cloned and transforming viruses in that it contained three or four size variants of EcoRI ABC het fragments. Possible involvement of the fragments in EA induction is noted. (22 Refs)

29. EXCISION OF POLYOMA VIRUS GENOMES FROM CHROMOSOMAL DNA BY HOMOLOGOUS RECOMBINATION.

Lania L, Boast S, Fried M
Istituto di Biologia Generale e Genetica, Universita di Napoli, Napoli, Italy
Nature; 295(5847):349-350 1982

Excision of polyoma virus genomes from chromosomal DNA was examined in five polyoma-transformed rat cell lines. One cell line contains multiple inserts of integrated viral sequences, free viral genomes and at least one complete early region containing an intact coding region for the polyoma large T antigen (T-Ag). Other four lines do not contain free viral forms or an intact coding region for the polyoma large T-Ag. All five lines contain intact coding regions for the small

and middle T-Ag species. All five lines were fused either to themselves or to mouse cells and the fused cells were assayed for free viral forms (at varying times) or the production of infectious virus (after 5 days). In the self-fused cells, free viral forms were found only in the polyoma-rat cells; no virus was detected (less than 50 plaque-forming units/10(6) cells) in the self fusion of the polyoma-rat cells. The production of both free viral genomes and infectious virus was detected after fusion to mouse cell of polyoma-rat and two lines containing partial duplications of viral sequences. In the two lines that did not contain partial duplications of viral sequences, no free viral forms or infectious virus could be detected after fusion to mouse cells. In the fusions of 2b-C3 and 53-rat with mouse cells, the amount of viral DNA and infectious virus produced appears to be related to the amount of duplicated viral sequences present, suggesting that the excision may be a function of the target size for possible recombination events as has been observed in other systems. (32 Refs)

30. SYNTHESIS AND STABILITIES OF PROTEINS RELATED TO THE POLYOMA SMALL T ANTIGEN IN ESCHERICHIA COLI.

Horwich A, Koop AH, Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Mol Cell Biol; 2(1):88-92 1982

Early proteins (T antigens) encoded by polyoma and simian virus 40 which are involved in virus replication and neoplastic cell transformation were found to also be synthesized in Escherichia coli. A protein with N terminus derived from polyoma was significantly more unstable than a similar protein with N terminus derived from beta-galactosaminidase. (6 Refs)

31. POLYOMA T ANTIGENS.

Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

Current knowledge on polyoma T proteins is reviewed, including the role of these viral-coded proteins in lytic infection of mouse cells, DNA nucleotide sequences (coding and regulatory signals), mutations affecting the T antigens, and cell transformation and tumorigenicity. The T antigens are compared structurally with SV40 in terms of nucleotide sequences. The roles of the large, small, and medium T antigens in lytic infection and transformation are discussed. The functions associated with small and medium T antigens, particularly attempts to detect protein kinase activity associated with polyoma T, are reviewed. (110 Refs)

32. ASSEMBLY OF ADENOVIRUS PENTON BASE AND FIBER.

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Virology; 116(2):589-604 1982

Human adenovirus Type 2 (H2) fiber isolated from the cellular pool of H2 wild-type (WT) soluble components was found to be capable of assembly in vitro with penton base obtained from the fiber-defective temperature-sensitive (ts) mutant H2 ts-125. This assembly occurred over a relatively broad range of pHs (5.5-9.0) and of ionic strengths (0.05-1.0). The extent of penton formation was estimated by two-dimensional immunoelectrophoresis. The legitimacy of the assembly in vitro was demonstrated by morphological, biochemical, and biological evidence. The assembly of the penton base with the fiber appeared to be a reversible reaction, with a dissociation constant KD = 2x10(-7) M, in terms of fiber molarity. This value implied a high affinity of the penton base for the fiber. Comparative digestions by carboxypeptidase of uncombined fiber and of penton base-combined fiber suggested that the recognition site for assembly involved the last 20 amino acids of the C-terminal sequence of the fiber polypeptide chain. The same analysis performed on [14C]glucosamine-labeled fiber and penton seemed to indicate that the carbohydrate units carried by the fiber were positioned too far from the C-end to be directly involved in the recognition and assembly process of the penton base with the fiber. Chimeric penton produced in vitro by incubating fiber and penton base from different adenovirus serotypes, as well as in vivo by interserotypic ts+ recombinants suggested a group specificity of the recognition site on the fiber and a likely highly conserved C-terminal amino acid sequence. Assembly of penton base and fiber in vitro resulted in a significant change in the antigenicity of the penton base-combined fiber, which was thought to reflect some three-dimensional remolding. (Author abstract) (25 Refs)

33. TRYPTIC AND CHYMOTRYPTIC METHIONINE PEPTIDE ANALYSIS OF THE IN VITRO TRANSLATION PRODUCTS SPECIFIED BY THE TRANSFORMING REGION OF ADENOVIRUS TYPE 2.

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Dept. Microbiology, Health Sciences Center, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Virology; 116(2):406-418 1982

Early region 1 (E1) cytoplasmic RNAs of adenovirus Type 2 were translated in vitro. Structural relationships between these proteins were then established by tryptic and chymotryptic digestion and two-dimensional peptide mapping. This analysis also allowed a direct comparison of these proteins with polypeptides isolated from early infected cell extracts and previously assigned to E1 by indirect means. E1a (0-4.5%) RNA encodes five proteins in vitro: 35K, 41K, 47K and 53K at early times, and a 28K protein at later times in infection. These five proteins are all highly related by peptide mapping analysis, and are also related to a group of four proteins isolated from cell extracts prepared early in infection. E1b (4.5-11.0%) early RNA encodes 52K and one or more 15K proteins in vitro. The 52K protein shares tryptic peptides with a 53K immunoprecipitated T antigen. A 15K protein shares some peptides with the 52K protein and with several proteins isolated from infected cells. At intermediate to late times, E1b RNA encodes a 12K protein that corresponds to the virion structural polypeptide IX. These data also permit the correlation of E1 proteins synthesized in vitro with the polypeptides predicted by E1 sequence analysis. (Author abstract) (45 Refs)

34. INTERACTION OF HERPES SIMPLEX VIRUS WITH HUMAN CELL LINES AT VARIOUS STAGES OF LYMPHOID DIFFERENTIATION.

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Intervirology; 16(1):33-42 1981

The growth of herpes simplex virus (HSV) Type 1 in human lymphoid cell lines, arrested at various stages of differentiation, was studied. The synthesis of viral DNA and antigens and the production of infectious virus were followed in null, B and T leukemia-lymphoma cell lines. It was found that while 'nondifferentiated' null cells and cells differentiating along the B path-

way, even at very early stages o f differentiation, supported HSV growth, cell lines of T origin at all stages of differentiation were generally nonpermissive. The failure of T cells to support the growth of HSV did not result from inefficient adsorption to the host cell. However, viral DNA synthesis was not detected, and a significant reduction in the ability to synthesize HSV antigens was observed. It is suggested that the block in the growth cycle of the virus occurs at a stage after adsorption of the virion to the cells, but prior to synthesis of its DNA and proteins. (Author abstract) (22 Refs)

35. THE MECHANISM OF GENETIC RESISTANCE TO MAREK'S DISEASE IN CHICKENS.

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Int J Cancer; 29(2):169-174 1982

Genetic resistance to Marek's disease in RPL line-6 chickens is expressed not only at the level of host immunological responses against virus and tumor antigens, but also at the level of target lymphoid cells for virus infection and transformation. The nature of the target cell involved was investigated. Spleen cells from susceptible line-7 chickens adsorbed more Marek's disease virus and turkey herpesvirus in vitro than line-6 spleen cells. In the case of Marek's disease virus this was reflected in the replicative ability of the virus in vivo. Transplantation of thymus fragments from 1-day-old line-7 chickens into thymectomized line-6 chickens conferred a high degree of susceptibility on the latter, but the transplantation of spleen or bursa fragments had no significant effect. The reverse procedure, ie grafting of line-6 thymi into line-7 chickens, did not diminish the susceptibility of the recipients. In each treatment group the observed titers of leukocyte-associated viremia correlated with the susceptibility of the group to Marek's disease. Histologically the grafted thymus fragments became depleted of lymphocytes immediately after transplantation. By 6 days there was substantial recovery, apparently as a result of repopulation of the thymic epithelium by host stem cells. This was confirmed by transplanting thymus fragments between individuals of opposite sexes. Karyotype analysis showed that the thymus contained lymphocytes of the sex of the recipient. However, karyotype analysis of lymphoma cells taken from recipient line-6 chickens that had received thymus grafts from line-7 birds of the opposite sex showed that, in the majority of cases, the lymphomas consisted of cells of donor origin. It is concluded that the susceptibility of line-7 chickens is largely attributable to the greater susceptibility of their T-lymphocytes to infection and transformation by Marek's disease virus, and that this susceptibility can be transferred to genetically resistant line-6 birds by adoptive transfer of the cells in the form of thymus fragments. (Author abstract) (16 Refs)

36. IDENTIFICATION OF EPSTEIN-BARR VIRUS STRAIN DIFFERENCES WITH MONOCLONAL ANTIBODY TO A MEMBRANE GLYCOPROTEIN.

Qualtiere LF, Chase R, Vroman B, Pearson GR
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Proc Natl Acad Sci USA; 79(2):616-620 1982

Two monoclonal antibodies directed against Epstein-Barr virus (EBV)-induced membrane antigens (MA) were isolated in this study. One of the monoclonal antibodies, designated 2F5.6, was an IgG2 which, as detected by membrane and fixed cell immunofluorescence, reacted with MA-positive lymphoblastoid cell lines that produced transforming EBV but not with the MA-positive P3HR-1 cell line that produced the lytic, nontransforming strain of this virus. This antibody precipitated the Mr 320,000/350,000 glycoprotein from B-95 virus infected cultures and the Mr 300,000 and 220,000/250,000 glycoproteins from Raji cells superinfected with P3HR-1 virus but did not precipitate any of these EBV-specific glycoproteins from the P3HR-1 cell line. In contrast, the second monoclonal antibody, IgM designated B10.3, reacted with all virus-producing cell lines including the P3HR-1 cell line. The identity of the glycoprotein that serves as the target for this antibody is still unknown. Neither antibody had neutralizing activity against the B-95 or P3HR-1 strain of EBV. These results indicated that the 2F5.6 monoclonal antibody was directed against an antigenic determinant on the major membrane glycoprotein which is common to transforming strains of EBV but absent from the lytic P3HR-1 strain whereas the B10.3 monoclonal antibody was directed against a group-specific EBV-induced membrane determinant. (Author abstract) (25 Refs)

37. CELL SURFACE PROPERTIES OF HLA ANTIGENS ON EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINES.

Smith LM, Petty HR, Parham P, McConnell HM
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Proc Natl Acad Sci USA; 79(2):608-612 1982

A number of monoclonal antibodies have been used to investigate the distributions and rates of lateral motion of the HLA-A,B, and -DR antigens on several Epstein-Barr virus-transformed B-cell lines. The lateral diffusion coefficients (D) of fluorescein conjugates of the monoclonal antibodies bound to the cell surface were determined by fluorescence recovery after pattern photobleaching. Ds of HLA-A and -B were found to be comparable and of the order of 10(-9) to 10(-10) cm2/sec for each of the seven monoclonal antibodies and four cell lines examined. The HLA antigens appear to be monomeric on the cell surface based on experiments using mixtures of arsanilic acid-conjugated and fluorescein-conjugated antibodies. Four monoclonal antibodies against DR antigens were examined. Two of these, Genox 3.53 and L243, labeled th e cell surface uniformly and gave Ds comparable to those obtained for the HLA-A and -B antigens. The other two, DA2 and 2.06, rapidly patched on the cell surface and were immobile. The DA2, L243, and Genox 3.53 antibodies bound outside of the caps formed with the arsanilic acid-conjugated 2.06 antibody and a second-step rhodamine-conjugated rabbit anti-arsanilate antibody. This is consistent with recent biochemical evidence that there are multiple distinct antigens coded for by the HLA-DR region. (Author abstract) (63 Refs)

38. EFFECT OF DIFFERENT EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS (EBNA, EA, AND VCA) ON THE LEUKOCYTE MIGRATION OF HEALTHY DONORS AND PATIENTS WITH INFECTIOUS MONONUCLEOSIS AND CERTAIN IMMUNODEFICIENCIES.

Szigeti R, Masucci MG, Henle W, Henle G, Purtilo D, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Clin Immunol Immunopathol; 22(1):128-138 1982

Leukocytes from healthy Epstein-Barr virus (EBV)-seropositive (SP) subjects show significant migration inhibition (LMI) with EBNA (EBV-determined nuclear antigen)-containing extracts derived from nonproducer, EBV-genome-carrying cells, or presented in the form of partially purified EBNA-prepara-

tions. Additional EBV antigens, EA and VCA, presented in the form of induced cell extracts do not add any measurable increase to their response. Leukocytes from acute infectious mononucleosis (IM) patients, on the other hand, do not respond to EBNA, but they show a good response to induced EA- or EA and VCA-containing cell extracts. This is in accordance with known differences in EBV-antibody pattern in healthy SPs as contrasted to acute IM patients. Leukocytes from chronic mononucleosis patients resemble those from acute IM patients in their preferential EA/VCA and deficient EBNA response in the LMI test. Cells from four X-linked lymphoproliferative disease (XLP) patients showed complete absence of reactivity to PHA and to EBV antigens in the LMI test, showing a general defect in cell-mediated immune responses. Leukocytes from a group of patients with lymphoproliferative malignancies in remission and elevated EBV-antibody titers showed a variety of responses, resembling normal SP donors, or IM patients, or showing a complete unresponsiveness in the LMI test. (Author abstract) (41 Refs)

39. EPSTEIN-BARR VIRUS SUSCEPTIBILITY OF B CELLS CORRELATES TO THE PRESENCE OF COMPLEMENT RECEPTORS BUT NOT SURFACE IMMUNOGLOBULINS.

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Intervirology; 16(2):118-122 1981

Nuclear antigen (EBNA) inducibility by Epstein-Barr virus (EBV) was assessed in relation to the presence of complement (C3) receptors and surface immunoglobulins (SIg) on leukemic lymphocytes. When erythrocyte-antibody-complement complex (EAC)-positive, SIg-negative B cells wer e exposed to EBV, EBNA synthesis occurred with a high frequency. In contrast, no significant EBNA induction was evident in SIg-positive, EAC-negative B cells. Cells possessing both markers were EBV-infectable, in proportion to the frequency of EAC-rosette formation. These data seem to indicate that EBV susceptibility of human B cells is closely related to the presence of C3 receptors but not SIg. Leukemic T cells and myelogenous leukemia cells were not EBV-susceptible, although some cells were significantly positive for C3 receptors. (Author abstract) (15 Refs)

40. ASSOCIATION OF VIRAL POLYPEPTIDES WITH THE NUCLEAR MATRIX FROM HERPES SIMPLEX VIRUS TYPE 2 INFECTED VERO CELLS (MEETING ABSTRACT).

Tsutsui Y, Hoshino M, Nishiyama Y, Maeno K
Department of Pathology, Nagoya University, Nagoya, Japan
Proceedings of the Japanese Cancer Association 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 413 pp., 1981.

The nuclear matrix has been shown to play an important role in the physiology of nuclear function. Recently it was reported that polyoma T-antigen associated with the nuclear matrix from lytically infected 3T3 cells. We examined whether viral polypeptides are associated with the nuclear matrix from the HSV2 infected Vero cells, because HSV2 has been linked with human cervical carcinoma in seroepidemiological studies. Analysis of polypeptides using sodium dodecyl sulfate-gel electrophoresis showed association of 130-140K viral polypeptide with the nuclear matrix as a major component and association of several viral polypeptides with it as minor components. The characterization of these proteins is in progress in relation to viral and cellular DNA replication. (no Refs)

41. ADENOVIRUS TYPE 12 T ANTIGEN-RELATED SURFACE ANTIGEN DETECTED BY IMMUNOFLUORESCENCE ON THE MEMBRANE OF TRANSFORMED AND INFECTED CELLS.

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Unit Virology, Gulbenkian Inst. Science, Apartado 14, P-2781 Oeiras Codex, Portugal
Virology; 117(1):135-145 1982

THA cells, derived from a hamster tumor induced by adenovirus type 12 (Ad12), were analyzed by immunofluorescence for the presence of virus-specific surface antigens. S antigen is a surface antigen detected on suspended living cells by a serum collected from hamsters immunized with Ad12. Besides S antigen, a new surface antigen (surface-T) was observed in formaldehyde-fixed cells treated with anti-T serum. Anti-T serum is not reactive against S antigen in living cells and anti-S serum did not detect surface-T antigen. The membrane location of surface-T antigen was confirmed with a Staphylococcus aureus binding assay. Surface-T antigen seems specific for Ad12, as it is not observed in hamster embryo cells, and is not recognized by antisera against SV40-or polyoma-T antigens nor by antiserum again st hamster embryonic antigens. Surface-T antigen is also seen in infected KB cells but not in abortively infected RK13 cells. Anti-P serum, raised against an extract of infected RK13 cells, failed to detect surface-T antigen. Experiments with adsorbed anti-T and anti-S sera confirmed the specificity of surface-T antigen and its distinctiveness from S antigen. (Author abstract) (22 Refs)

42. IMMUNOGLOBULIN SECRETING B LYMPHOBLASTS GROWN AND CLONED FROM WITHIN TUMOUR TISSUE FROM MELANOMA PATIENTS (MEETING ABSTRACT).

Watson DB, Mackay IR
No affiliation given
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Experiments were designed to produce human monoclonal antibodies reactive with antigens associated with and specific to melanoma cells. The approach entailed the use of Epstein-Barr virus (EBV) to transform B lymphocytes into proliferating B lymphoblastoid lines which could then be cloned. As the most likely source of specifically tumor reactive B lymphocytes, the EBV was added to a cell suspension from freshly resected melanoma. In this way 5 B lymphoblastoid cells lines have been established from within the tumor tissue of four patients. It has been demonstrated that these Epstein-Barr virus nuclear antigen (EBNA) positive lines secrete immunoglobulin and the kinetics of growth and secretion have been established. Two of these lymphoblastoid lines secreted immunoglobulin reactive with fresh autologous melanoma cells as well as melanoma cell lines. These lines have been cloned and are currently being expanded with the intention of producing large amounts of monoclonal anti-melanoma cell antibody. It is of interest that in two patients EBNA-positive B lymphoblastoid cells grew spontaneously from primary cultures of tumor tissue without contact with exogenous EBV. In contrast to normal subjects, T lymphocytes from the peripheral blood of these two patients were completely unable to mount an induced cell-mediated response against autologous B lymphoblasts, findings which demonstrate a degree of T cell incompetence. (no Refs)

43. B LYMPHOBLAST ANTIGEN (BB-1) EXPRESSED ON EPSTEIN-BARR VIRUS-ACTIVATED B CELL BLASTS, B LYMPHOBLASTOID CELL LINES, AND BURKITT'S LYMPHOMAS.

Yokochi T, Holly RD, Clark EA
(c/o Clark) Regional Primate Res. Center and Dept. Genetics, Univ. Washington, Seattle, WA, 98195
J Immunol; 128(2):823-827 1982

Two new cell surface antigens expressed on B lymphoblastoid cell lines (B-LCL) were defined with cytotoxic mouse monoclonal antibodies. One marker, BB-1 (for B lymphoblast antigen-1), was detected on human and nonhuman primate B-LCL, Epstein-Barr virus (EBV)-activated B cell blasts, most Burkitt's lymphomas, and Ia+ B lymphoblast-like myelomas. Polyclonal B cell activators such as pokeweed mitogen (PWM) and lipopolysaccharide (LPS) also induced the expression of BB-1 on immunoglobulin (Ig)-positive cells.In contrast, BB-1 could not be detected on normal lymphoid tissues by complement-dependent cytotoxicity and immunofluorescence (IF) assays or by analysis with a fluorescence-activated cell sorter (FACS). T cell blasts, T cell leukemias, and pre-B cell or erythroblastic leukemia cell lines were also BB-1 negative. Of particular interest was the finding that BB-1 was expressed on the Jijoye lymphoma but only marginally on a subline of Jijoye, P3HR-1, that lacks receptors for EBV and produces a defective virus incapable of transforming lymphocytes. A second lymphoblast antigen (LB-1) unlike BB-1, was present on both T and B cell blasts and virus-transformed T- and B-LCL but not on normal lymphoid tissues. (Author abstract) (50 Refs)

44. IMPROVED IMMUNOFLUORESCENCE ANTIGENS FOR DETECTION OF IMMUNOGLOBULIN M ANTIBODIES TO EPSTEIN-BARR VIRAL CAPSID ANTIGEN AND ANTIBODIES TO EPSTEIN-BARR VIRUS NUCLEAR ANTIGEN.

Gallo D, Walen KH, Riggs JL
Viral and Rickettsial Disease Lab., California Dept. Health Services, Berkley, CA, 94704
J Clin Microbiol; 15(2):243-248 1982

Epstein-Barr viral capsid antigen (VCA) and nuclear antigen produced by modified procedures were evaluated for use in measuring VCA IgM and Epstein-Barr virus (EBV) nuclear antigen antibody responses in sera from patients with EBV infection. VCA production was stimulated with a phorbol ester, and the EBV nuclear antigen (EBNA) cells were fixed in suspensions to eliminate loss of antigen during the drying process. Approx 70% of the tumor-promoter agent-stimulated P3HR-1 cells fluoresced when reacted with VCA-IgM- or VCA-IgG-positive sera. In the anticomplement immunofluorescence test for EBNA antibody, 100% of the cells (except the dead ones) in every smear tested showed dense nuclear fluorescence with positive sera. The improved antigen preparations were evaluated in tests on 122 sera. Twenty patients possessed antibody patterns consistent with recent EBV infection. Fifteen patients showed VCA-IgM antibody and no antibody to EBNA; both IgM and EBNA antibodies were present in later specimens taken form five patients. Patients examined in the study were heterophil negative and all were diagnostic problem cases. Patients presenting with lymphatic disease who are heterophil negative and for whom other infections have been ruled out are diagnostic problems for the clinician, especially when lymphoma is a possibility. Reliable serological tests for EBV should be helpful for studying these problem cases. (18 Refs)

45. RESTRICTED HEL-12 VIRUS INFECTION IN DE NOVO INFECTED HUMAN AND CANINE CELLS.

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Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, Bethesda, MD, 20205
J Gen Virol; 57(part2):343-355 1981

Model systems to study restricted primate retrovirus expression were established by de novo infection of canine fetal thymus cells (CF-2Th) and superinfection of HEL-12 cells with HEL-12 virus. In the resulting CF-2Th/HEL-12V cells and HEL-12/HEL-12V cells, four sequential stages of virus infection were defined by the production of reverse transcriptase (RT)-containing particles and expression of virus antigens as detected by radioimmunoassays. Stage I cells did not synthesize virus antigens or produce RT-containing particles. Stage 2 cells synthesized virus antigen but not RT-containing particles. Stage 3 cells synthesized antigen and produced RT-containing particles, and Stage 4 cells synthesized virus antigens but no longer produced RT-containing particles. The duration of the four stage infection is 2 to 3 weeks in both cell types. Monospecific competition radioimmunoassays to detect HEL-12V p 30 or gp70 antigen showed high levels of virus antigen throughout Stages 2 to 4 of infection. Analysis of immunoprecipitates formed under conditions to detect either p30-or gp70-containing proteins in cells pulsed and pulsed-chased with [3H]leucine showed the same spectrum of virus precursor polyproteins, intermediates and mature virion components in Stage 2 to 4 cells in canine and human infections. Spent culture fluids collected from Stage 3 and Stage 4 CF-2Th/HEL-12V cells failed to reveal inhibitors of RT activity. Stage 4 CF-2Th/HEL-12V or HEL-12/HEL-12V cells labelled with [3H]uridine produced virions which incorporated [3H]uridine but did not have RT activity, suggesting that restricted infection is characterized by production of HEL-12V defective in RT activity. (Author abstract) (25 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

46. DETECTION OF TYPE-SPECIFIC ANTIGENIC DETERMINANTS OF MURINE MAMMARY TUMOR VIRUSES WITH CELL-MEDIATED IMMUNE ASSAYS.

Lopez DM, Sigel MM, Schlom J
Univ. Miami, Miami, FL, 33101
Proc Soc Exp Biol Med; 169(1):144-148 1982

Cell-mediated immune assays were used to detect type differences among mouse mammary tumor viruses (MMTV) obtained from various mouse strains. The diversity of MMTVs found and their recognition by the lymphoid cells may explain variations in mouse mammary tumor development and differences in their metastatic potential. (23 Refs)

47. PROPERTY OF MOUSE ENDOGENOUS C TYPE VIRUS ACTIVATED BY ADENOVIRUS CARCINOGENESIS (MEETING ABSTRACT).

Ohmori M, Kobayashi S, Ogawa K
Department of Pathology, Okayama University Medical School, Okayama, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Endogenous C type virus of C3Hf mice is activated by adenovirus carcinogenesis a nd this virus induces lymphoma. The density of purified C particles is 1.15-1.18 by RbCl density gradient analysis, and has the antigen common to leukemia viruses Gross-MuLV, Molony-MuLV, Rauscher-MuLV P30, AKR-LV P30, and FeLV P27 by immunodiffusion reaction. Its structural proteins, P30, is the main band, and P70, P59, P43, P15 and smaller ones reveal minor bands by sodium dodecyl sulphate-polyacrylamide gel electrophoresis. From these results it is assumed that this virus has a property different from known oncorna viruses. (no Refs)

48. A T-CELL LINE DERIVED FROM NORMAL HUMAN CORD LEUKOCYTES BY CO-CULTURING WITH ADULT T-CELL LEUKEMIA (ATL) CELLS: IMMUNOFLUORESCENT AND ELECTRON MICROSCOPIC STUDIES (MEETING ABSTRACT).

Miyoshi I, Yoshimoto S, Kubonishi I, Shiraishi Y, Akagi T, Ohtsuki Y, Hinuma Y
Department of Medicine, Kochi Medical School, Kochi, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

ATL cells from a female patient and cord WBC from a normal male infant were co-cultured and a T-cell line (MT-2) of cord WBC origin was established. The MT-2 line was E+, EA-, EAC-, SIg-, anti-T+, Ia+ and EBNA-. MT-2 cells had a normal male karyotype but were tumorigenic in newborn hamsters. The majority of MT-2 cells were reactive with sera from ATL patients in indirect immunofluorescence. Electron microscopy of MT-2 revealed numerous C type virus particles in the extra-cellular spaces. The origin and role of the virus in transformation of normal human cord T-cells and currently under investigation. (no Refs)

49. STRUCTURAL DOMAINS OF ENDOGENOUS MURINE LEUKEMIA VIRUS GP70S CONTAINING SPECIFIC ANTIGENIC DETERMINANTS DEFINED BY MONOCLONAL ANTIBODIES.

Pinter A, Honnen WJ, Tung JS, O'Donnell PV, Hammerling U
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Virology; 116(2):499-516 1982

Eight distinct antigenic determinants, or epitopes (labeled a-h) were identified on endogenous ecotropic murine leukemia virus (MuLV) gp70s using a series of murine and rat monoclonal antibodies. These epitopes were characterized by their distribution patterns in a panel of cloned MuLVs, and by their localization in fragments of gp70 generated either by spontaneous breakdown of purified gp70, or by controlled proteolysis of gp70 in solubilized virions. A major 34K carboxy terminal fragment was formed which contained epitopes b, c, and f. This fragment also possessed the p15(E) disulfide linkage site, and contained approximately four complex (Type I) carbohydrate chains. An amino terminal 35K fragment contained epitopes a, d, g, and h, and possessed two glycosylated sites, including a site which occasionally retained an endoglycosidase H-sensitive oligosaccharide chain. A related 49K fragment was also obtained which included t he entire 35K region and contained an additional sequence bearing epitope e. In a series of dualtropic MCF-type viruses studied, only those epitopes located in the 32K fragment were ever retained, indicating that for these recombinant viruses at least a portion of that domain was derived from the ecotropic parent. A model is presented indicating the likely orientation of these fragments and their structural characterisiics. (Author abstract) (38 Refs)

50. ENDOGENOUS MURINE LEUKEMIA VIRUS-ENCODED PROTEINS IN RADIATION LEUKEMIAS OF BALB/C MICE.

Tress E, Pierotti M, DeLeo AB, O'Donnell PV, Fleissner E
(c/o Fleissner), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Virology; 117(1):207-218 1982

To explore the role of endogenous retroviruses in radiation-induced leukemogenesis in the mouse, we have examined virus-encoded proteins in nine BALB/c leukemias by pulse-chase labeling procedures and serological typing with monospecific and monoclonal antibodies. The major gag precursor protein, Pr65gag, was observed in all cases, but only three leukemias expressed detectable amounts of the glycosylated gag species, gP95gag, or its precursor, Pr75gag. No evidence was found for synthesis of gag-host fusion proteins. None of the leukemias released infectious xenotropic or dualtropic virus, but all nine expressed at least one env protein with xenotropic properties. In two instances a monoclonal antibody, 35/56, which is specific for the MuLV GIX antigen, displayed a distinctive reactivity with this class of env protein, although this antibody is unreactive with replicating xenotropic viruses. An ecotropic/xenotropic recombinant env protein with the same 35/56 phenotype was observed in a leukemia induced by a strongly leukemogenic virus isolated from a BALB/c radiation leukemia. (Author abstract) (40 Refs)

51. IMMORTALIZATION OF ANTIGEN SPECIFIC, HELPER T CELL LINES BY TRANSFORMATION WITH THE RADIATION LEUKEMIA VIRUS (RADLV).

Yefenof E, Azar Y, Eidelsztein P, Ben-Sasson SZ
Lautenberg Center General and Tumor Immunology, Hebrew Univ-Hadassah Medical Sch., P.O.B 1172, Jerusalem, Israel
J Immunol; 128(2):625-628 1982

Antigen-specific immune T lymphocytes of male C57BL/6 mice were enriched in vitro on monolayers of antigen-pulsed syngeneic macrophages. The cells were treated in vitro with RadLV and inoculated intrathymically into irradiated female C56BL/6 animals. Thymomas arising in the inoculated recipients were characterized as donor- (male) type according to their karyotype. In vivo and in vitro cell lines were established from the primary lymphomas, two of which (designated ROT/6.1 and ROT/6.2) were capable of providing antigen- (carrier) specific help in normal or preimmunized mice. None of the lymphomas could induce antigen-specific DTH reaction. Five months after their establishment, ROT/6.2 al one retained its carrier specificity. ROT/6.2 consisted mainly of Lyt-1+ cells, whereas the ROT/6.1 population was more heterogeneous and contained Lyt-1+, Lyt-2+, and Lyt-3+ cells. The carrier specificity of the latter may have been lost due to selection against the specific helper cells during prolonged passages. (Author abstract) (18 Refs)

52. CHARACTERIZATION AND ANTIGEN DETECTION OF TUMOR CELL LINE FROM CHICKEN WITH LYMPHOID LEUKOSIS (MEETING ABSTRACT).

Ishizaki R, Jono M
Nippon Medical School at Sakuragi, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

One of the established cell lines, 1104B, which was obtained from Dr Hihara, National Institute of Animal Health, has been characterized as lymphoblastic B cell type, having Fc receptor, and producing IgA. No Forssman antigen was found on the cell. The virus in cell culture fluid was detected by 3H-uridine incorporation at a density of 1.16g/ml by ultracentrifugation in sucrose gradient. Immuno-precipitation experiment with lysate of the cell labeled with 35S-methionine, revealed two unique polypeptides having mol wt 200x and 45x10(3) dalton respectively, with anti-IgM serum. (no Refs)

53. ANALYSIS OF SHARED ANTIGENS OF TUMORS INDUCED BY FELINE SARCOMA VIRUS IN RATS AND THOSE IN CATS (MEETING ABSTRACT).

Maruyama K, Fukushima T, Nakajima Y, Mochizuki S, Miyauchi M, Kawamura K
Department of Pathology, Chiba Cancer Center Research Institute, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

By the cytotoxicity test, tumors (RFeSV-T) induced by feline sarcoma virus of Snyder-Theilen strain (FeSV) in inbred Wistar rats have been demonstrated to carry antigens capable of evoking in syngeneic rats humoral as well as cellular antibodies cytotoxic to not only RFe-SV-T cells but also FeSV-induced cat tumor (FeSV-T) cells. In an attempt to isolate shared antigens in RFeSV-T and FeSV-T, polypeptides of [35S]methionine-labeled virus in FeSv-T were analyzed by the immunoprecipitation with the serum from rats immunized with RFeSV-T and then by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Several mol wt species including p70, p46, p30, and p15 were found immunoprecipitated and present in both RFeSV-T and FeSV-T. Their role in tumor immunity is under our current investigation. (no Refs)

54. THE SAME GENETIC LOCUS DIRECTS DIFFERENTIATION-LINKED EXPRESSION OF ENDOGENOUS RETROVIRUS GP70 ON THYMOCYTES AND SPLEEN CELLS IN THE MOUSE.

Tung JS, Shen FW, Viamontes G, Palladino M, Fleissner E
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 15(1):103-108 1982

Expression of the major envelope glycoprotein (gp70) of murine leukemia virus (MuLV) was studied in spleen cells of C57BL/6 (B6) and 129 mice that are negative for thymocytes surface antigen (GIX) and spleen cells of their congeneic GIX+ and GIX- derivatives. Proteins with a mol wt of approx 70,000 daltons were specifically recognized by a group-specific anti-gp70 serum in spleen cell lysates of 129, B6, and B6-GIX+ mice; 129-GIX- cells were negative. A monoclonal antibody specific for GIX+ MuLV gp70 precipitated the same gp70 molecules on spleen cells from the GIX+ strains. Occurrence of spleen cell gp70 in these strains appeared to controlled by the same genetic locus (Gv-1) that determines the presence of GIX+ gp70 on thymocytes. The presence of gp70 on spleen cells from B6-nu mice as well as on cytotoxic spleen T cells indicated that gp70 molecules are expressed by both T and non-T cells. (15 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

55. GENETIC CONTROL OF SENSITIVITY TO MOLONEY LEUKEMIA VIRUS IN MICE: V. ROLE OF H-2-LINKED GENES IN THE CONTROL OF ANTI-FMR CYTOLYTIC T-LYMPHOCYTES.

Duprez V, Debre P, Levy JP
Laboratoire Immunologie et Virologie des Tumeurs, INSERM U 152, Hopital Cochin, Paris 14e, France
Cell Immunol; 65(2):317-324 1981

Three H-2-linked genes, Rmv1, Rmv2, and Rmv3 control the resistance of mice against Moloney virus (MLV)-induced leukemias. It has been shown previously that they function as immune response (Ir) genes regulating the level of antivirus antibodies. In the present experiments, the cell-mediated antitumor response has been studied in a series of inbred strains selected for their resistance or sensitivity to the MLV-induced disease. We failed to detect any relationship between resistance and sensitivity and the ability to produce cytolytic T lymphocytes (CTL) directed against the virus-induced FMR cell surface antigen. Furthermore, the role of each Rmv gene has been studied separately using congenic pairs of mice differing at only one of these loci: we failed to evidence any influence of these genes in the cell-mediated antitumor reactions as measured by the ability to lyse syngeneic FMR(+) target cells. Nevertheless a gene mapping in the D region of the MHC but probably different from RMv3 controls the response of a subset of anti-FMR CTL restricted by the H-2Kk antigens, with higher response in H-2Dd animals than in H-2Db animals. This observation confirms the existence of H-2D region associated Ir genes regulating the CTL-mediated antitumor immune responses by choosing the subset of responder CTL, and suggests that a fourth H-2-linked gene plays some role in the genetic control of the anti-FMR immune response. (Author abstract) (15 Refs)

56. SPECIFIC THYMUS-DERIVED (T) CELL RECOGNITION OF PAPOVA VIRUS-TRANSFORMED CELLS.

Greene MI, Perry LL, Kinney-Thomas E, Benjamin TL
Dept. Pathology, Harvard Medical Sch., 25 Shattuck St., Boston, MA, 02115
J Immunol; 128(2):732-736 1982

As a first step toward identifying papova virus-specific transplantation antigens and characterizing the immune response to these antigens, a series of congenic B10 mouse lines transformed by polyoma virus and SV40 has been obtained. B10.D2 (H-2d) mice immunized with x-irradiated polyoma-transformed B10.D2 cells (PyB10.D2) contained within their spleens a population of T cells that upon restimulation in vitro preferentially lyse 51Cr-labeled PyB10.D2 compared with other allogeneic polyoma-transformed target cells or SV40-transformed B10.D2 cells. Twenty hr after acute infection with polyoma virus, SV10.D2 cells express cell surface structures recognizable by polyoma-specific CTL. This CTL activity is therefore both polyoma specific and H-2 restricted, indicating associative recognition of H-2 molecules along with the virus-specific antigen. (Author abstract) (39 Refs)

57. THE MECHANISM OF MODULATION OF HUMORAL IMMUNE RESPONSES AFTER INFECTION OF MICE WITH LACTIC DEHYDROGENASE VIRUS.

Isakov N, Feldman M, Segal S
Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel
J Immunol; 128(2):969-975 1982

The effect of infection with lactic dehydrogenase virus (LDV) on the humoral immune response was investigated using sheep erythrocytes (SRBC) as a test antigen. We found that immunization of mice with SRBC simultaneous with LDV infection resulted in an augmented splenic immune response characterized by an increase in the number of specific antibody-producing cells (APC). This augmentation was mainly restricted to the subpopulation of APC that produces antibodies of the IgG2 isotype. A similar augmentation was obtained in the secondary response, provided that infection with LDV took place at the stage of memory induction. In contrast to the effect on spleen APC, the peripheral blood revealed no change or even a slight reduction in the titer of antibodies directed against SRBC. We found that the virus does not affect the in vitro induced humoral response, and therefore the observed in vivo augmentation is probably not attributable to a direct activation of lymphocytes. Since the infection with LDV is followed by splenomegaly, the observed increase in splenic APC could be a result of a regulatory defect in the inflammation processes that causes enhanced trapping of cells in the spleen. Testing this possibility, we indeed found an enhanced trapping in the spleen of both lymphocytes and exogenous radiolabeled SRBC. In contrast, measurements of the 125I-IdUrd that was incorporated into the spleen cells indicated that LDV does not augment activation and proliferation of splenic lymphocytes. On the basis of these results, we assume that the changes i n the humoral responses observed in LDV-infected mice may result from changes in regulation of trapping and sequestration of cells in the lymphatic organs. These processes are most probably controlled by reticuloendothelial cells, which were shown to serve as target cells for LDV. Thus, the widely observed augmentation of the splenic APC response in LDV-infected mice may result from the accumulation in the spleen of both lymphocytes and antigen (SRBC) and should not be attributed to an adjuvant-like activity of LDV, the accepted assumption. (Author abstract) (37 Refs)

58. ABNORMAL ANTI-EPSTEIN BARR VIRUS ANTIBODIES IN CARRIERS OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME AND IN FEMALES AT RISK.

Sakamoto K, Seeley JK, Lindsten T, Sexton J, Yetz J, Ballow M, Purtilo DT
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J Immunol; 128(2):904-907 1982

The asymptomatic hemizygous female carriers of the x-linked lymphoproliferative syndrome (XLP) have abnormal antibody responses to EBV. This suggests partial expression of the defect that leads to EBV-provoked life-threatening diseases in their affected sons. EBV specific antibodies were measured in 65 serum samples of 12 obligate carrier females and 7 of their daughters (females at risk) during periods ranging from 1 to 5 yr. Abnormal qualitative antiviral capsid antigen (VCA) IgG titers were nearly fourfold higher than normal controls, two carriers had persistent IgM anti-VCA antibody, two-thirds had persistent IgA anti-VCA antibody, and half of the women had titers to early antigen (EA). Five of seven females exhibited a similar persistent pattern. In contrast, none of the unaffected family members nor 23 normal controls expressed IgA or IgM titers to VCA even with high exposure to the virus, and anti-EA was detected in only one control. Therefore, these findings may prove useful for detecting carriers of the syndrome. Abnormal anti-EBV titers similar to the carrier pattern have been reported in patients and other immunosuppressed individuals, and are indicative of active viral infection. (Author abstract) (31 Refs)

59. KINETICS OF THE IMMUNE RESPONSE OF TUMOR-BEARING HAMSTERS TO TWO SIMIAN VIRUS 40 CODED NON-STRUCTURAL POLYPEPTIDES PRESENT IN SIMIAN VIRUS 40 TUMOR CELLS.

Ransom JH, Thompson DL, Tevethia SS
(c/o Tevethia) Dept. Microbiology and Specialized Cancer Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Int J Cancer; 29(2):217-222 1982

The kinetics of the immune response of hamsters transplanted with virus-free SV40 tumor cells (TSV5) to two SV40-coded non-structural proteins of 94,000 daltons (T antigen) and 17,000 daltons (T antigen) was studied in order to determine if the variation in the immune reactivity of serum from tu morbearing animals towards these proteins can be explained on the basis of differential immune response during various stages of tumor growth. The results demonstrate that individual animals vary in their capacity to respond immunologically to T and t antigens in SV40-transformed cells and that, further, the immune response to T and t antigens is influenced by the stage of tumor development. (Author abstract) (31 Refs)

60. SYNGENEIC AND ALLOGENEIC CELL-MEDIATED CYTOTOXICITY AGAINST MAREK'S DISEASE LYMPHOBLASTOID TUMOR CELL LINES.

Schat KA, Shek WR, Calnek BW, Abplanalp H
Dept. Avian and Aquatic Animal Medicine, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Int J Cancer; 29(2):187-194 1982

Cell-mediated cytotoxicity (CMC) of lymphocytes obtained from chickens infected with Marek's disease (MD) virus against allogeneic MD lymphoblastoid cell lines has been reported by several research groups. Recently, we established a number of cell lines from MD tumors obtained from highly inbred chickens and characterized for major and minor histocompatibility antigens. Allogeneic versus syngeneic CMC was studied using those cell lines and lymphocytes obtained from chickens 6-8 days post infection with SB-I, a non-oncogenic MD virus. Allogeneic cytotoxicity could be easily demonstrated, while syngeneic cytotoxicity was a rare event. However, increase of the CMC assay period from 4 to 8 hr did enhance syngeneic cytotoxicity. Cold inhibition assays demonstrated that the allogeneic cytotoxicity was directed against alloantigens present on spleen lymphocytes sharing the same major histocompatibility antigens as the target cells. Cytotoxicity was not influenced by the sex of either target or effector cells or by the level of virus infectivity of the effector cells. (Author abstract) (32 Refs)

61. IMMUNIZATION AGAINST INFLUENZA IN CHILDREN WITH CANCER: RESULTS OF A THREE-DOSE TRIAL.

Brown AE, Steinherz PG, Miller DR, Armstrong D, Kellick MG, Gross PA, Davis AE
Memorial Sloan-Kettering Cancer Center, New York, NY
J Infect Dis; 145(1):126 1982

Immunization against influenza is recommended for children with neoplastic diseases despite poor immunogenicity in those receiving concomitant chemotherapy. The data show that a third dose of trivalent influenza virus vaccine does not significantly increase the number of children receiving chemotherapy who achieve HAI antibody titers of greater than or equal to 1:32 regardless of the vaccine antigen. Children with cancer who were not receiving chemotherapy achieved HAI antibody titers of greater than or equal to 1:32 with the same frequency as did normal children in the national study. These results confirm previous studies that show that primary immunization with influenza virus vaccine often is not immunog enic in children with neoplastic diseases who are receiving concomitant chemotherapy. The 'recall of the old antigen' (A/Texas/1/77 [H3N2]) is less hampered by the chemotherapy status. Other methods of immunization, such as adjusted schedules of immunization and, possibly, adjuvants and immunopotentiators, should be examined to determine how to immunize cancer patients successfully against newer strains of influenza virus. (Author abstract) (3 Refs)

62. PERSISTENCE OF ANTIBODY AFTER THE ADMINISTRATION OF INFLUENZA VACCINE TO CHILDREN WITH CANCER.

Sumaya CV, Williams TE
Dept. Pediatrics, Univ. Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX, 78284
Pediatrics; 69(2):226-229 1982

Children with cancer who received an intramuscular injection of inactivated split or whole bivalent (A/New Jersey/76-A/Victoria/75) influenza virus vaccine during the fall of 1976 were tested up to 18 mo later for the persistence of antibody. Titers of antibody greater than or equal to 10 to influenza A/New Jersey/76 virus were present in the sera of 34 children 2 wk after immunization. The geometric mean titer was 40.0. Eighteen mo later a titer greater than or equal to 10 was present in 13 (38%) children; the geometric mean titer was 8.5. Of 36 children with a titer of antibody greater than or equal to 10 to A/Victoria/75 virus 2 wk after immunization, 34 still had a detectable titer in the later examination. The geometric mean titer declined from 65.3 to 25.6. Titers of antibody to B/Hong Kong/72 virus (not included in the vaccine) remained relatively stable. In 11 children the usual chemotherapy was discontinued during the study. The shorter persistence of antibody to A/New Jersey/76 virus, in contrast to that of the other two influenza viruses tested, was associated with a lack of prior exposure to the virus and the absence of subsequent natural infection with this virus or an antigenically related subtype. The potential effect of cancer chemotherapy on the persistence of antibody levels is unclear. (Author abstract) (18 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

63. MECHANISM OF INTERFERON ACTIVITY. STABILITY AND TRANSLATION OF SIMIAN VIRUS-40 EARLY MRNA CODING FOR T-ANTIGEN IS COMPARABLE IN UNTREATED AND INTERFERON-TREATED MONKEY CELLS.

Daher KA, Samuel CE
Section Biochemistry and Molecular Biology, Dept. Biological Sciences, Univ. California, Santa Barbara, CA, 93106
Biochem Biophys Res Commun; 101(2):697-703 1981

Effects of interferon (IF)-treatment on the translation and functional stability of Simian virus 40 (SV40) early messenger (m)RNA coding for T-antigen under conditions where SV40 early RNA synthesis is apparently unaffected by IF were investigated. African green monkey kidney cells were infected with a tsA mutant of SV40 at an elevated temperature (40 C). The rate of T-antigen synthesis in tsA-infected cells at varying times following the addition of 1 ug/ml actinomycin D to the medium 36 hr post infection was determined to decide whether the stability of SV40 early mRNA differed between untreated and IF-treated cells. The SV40 mRNA coding for T-antigen had a half-life of about 3 hr, and there was no significant difference between the IF-treated and untreated cells. The fact that the decay of SV40 early RNA is indistinguishable between the IF-treated and untreated cells was thought to augment other facts and indicate that an enhanced degradation of SV40 early RNA by an IF-mediated RNAase probably does not play a major role in the antiviral action of IF in SV40 lytic infections. (25 Refs)

64. CHEMOTHERAPY (ADRIAMYCIN LEVAMISOLE) IN PRIMARY HEPATIC CANCER.

Diaz-Rubio Garcia E, Martin-Jimenez M, Diaz-Rubio Garcia M
Departamento de Medicina Interna, Unidad de Quimioterapia, Facultad de Medicina, Madrid, Spain
Oncologia; 6(6):215-223 1981

Adriamycin (AM) and levamisole (LE) therapy were evaluated in 20 selected patients (13 men, 7 women; 40-80 yr old) with primary hepatic cancer (PHC). Liver cirrhosis was present in 85% of the patients and metastasis (Me) in 30%. Results of test for alpha-fetoprotein were positive in 65% of the patients and results of tests for hepatitis B surface antigen (HbsAg) were positive in 60%. The AM (75 mg/square meter, iv, every 3 wk) and the LE (150 mg/day, 3 days/wk) were administered in at least two cycles. Two patients died during the 1st mo. The reactions to therapy were as follows: 11 progressions, 4 stabilizations, 5 partial remissions, and no complete remissions. The av survival time was 12.5 wk; for the patients with partial remission, the survival time was 32 wk, and for the patients with progression it was only 6 wk. Immunity was studied in 20 healthy controls and in the PHC patients, before the start of therapy and 1 mo later, using the following cutaneous tests: tuberculin, mumps antigen, 2,4-dinitrochlorobenzene (DNCB), and picryl chloride. The results of the tests using tuberculin were positive in two patients before therapy and in seven 1 mo later. All patients were negative to mumps before therapy, but five were positive 1 mo later. Two patients were positive to DNCB before therapy and five after. All patients were negative to picryl chloride before therapy, but four became positive 1 mo later. (46 Refs) (In SPA)

65. EFFECT OF PROTEASE INHIBITORS ON THE ACTIVATION OF EPSTEIN-BARR VIRUS REPRESSED IN CULTURED LYMPHOID CELLS.

Moriguki T, Sugawara K, Ito Y
(c/o Ito) Dept. Microbiology, Faculty of Medicine, Kyoto Univ., Kyoto 606, Japan
Intervirology; 16(1):49-52 1981

The effects of five microbial and one synthetic protease inhibitor on the activa tion of Epstein-Barr virus expression in latently infected lymphoblastoid cells were studied. All protease inhibitors tested suppressed both viral antigen induction by 5-iododeoxyuridine treatment and cell growth in general. Among the inhibitors, however, antipain and pepstatin exerted a relatively strong and significant suppressive effect on antigen induction as compared to their inhibitory effect on cell growth. (Author abstract) (11 Refs)

66. INHIBITORY EFFECT OF RETINOIDS ON EPSTEIN-BARR VIRUS INDUCTION IN RAJI CELLS.

Zeng Y, Zhou HM, Zu SP
Inst. Viroiogy, Chinese Academy Medical Sciences, Beijing, People's Republic of China
Intervirology; 16(1):29-32 1981

Induction of Epstein-Barr virus (EBV) early antigen after treatment with various combinations of croton oil and n-butyrate was markedely inhibited by retinoids 7901, 7902, Ro 10-9359 and Ro 11-1430. Possible administration of retinoids to virus capsid antigen IgA antibody-positive individuals in high-risk areas for nasopharyngeal carcinoma to prevent EBV activation and development of this cancer is discussed. (Author abstract) (12 Refs)

OTHER RELATED STUDIES

67. ADHERENT IA+ MURINE TUMOR LINES WITH CHARACTERISTICS OF DENDRITIC CELLS. I. MORPHOLOGY, SURFACE PHENOTYPE, AND INDUCTION OF SYNGENEIC MIXED LYMPHOCYTE REACTIONS.

Cohen DA, Kaplan AM
Dept. Surgery, MCV/VCU Cancer Center, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA, 23298
J Exp Med; 154(6):1881-1898 1981

Several adherent cell lines cloned from mouse P388 leukemia were isolated and characterized. The cell lines were morphologically and functionally similar to dendritic cells (DC) of the spleen with respect to dendritic processes, large numbers of mitochondria, surface expression of immune region-associated (Ia) antigens, and induction of syngeneic and allogeneic mixed lymphocyte reactions. Of adherent P388 cells, 24-69% were positive for Ia antigen, greater than 95% were positive for major histocompatibility D, splenic macrophage-associated, and T cell-associated antigens, and 0% were positive for surface immunoglobulins; positive values were obtained in 13-42%, greater than 95 %, 0, greater than 95%, and 0%, respectively, of nonadherent cells. Both adherent and nonadherent forms of P388 expressed Ia antigens, with a broad range of fluorescent intensity within each respective clone. Cell-to-cell variability of surface Ia antigens in both adherent and nonadherent cells was also detectable with antisera against I-A subregion antigens. Adherent cells strongly stimulated syngeneic and allogeneic T lymphocyte proliferation in the absence of antigen; cytotoxic T cells directed against the stimulators were induced only during allogeneic stimulation. Nonadherent P388 clones did not stimulate either allogeneic or syngeneic T cell proliferation. (28 Refs)

68. IDENTIFICATION OF A BALB/C H-2LD GENE BY DNA-MEDIATED GENE TRANSFER.

Goodenow RS, McMillan M, Orn A, Nicolson M, Davidson N, Frelinger JA, Hood L
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Science; 215(4533):677-679 1982

Gene transfer and immunoselection were used in the identification of a BALB/c genomic clone containing an H-2Ld gene (clone 27.5). Transformation of thymidine kinase-negative C3H mouse L cells with the cloned 27.5 DNA together with the herpes simplex virus tk gene produced transformants expressing Ld molecules detected by radioimmune assay with monoclonal hybridoma antibodies to Ld antigens. The foreign Ld gene products expressed by cloned mouse L cell transformants were shown to be virtually indistinguishable from BALB/c spleen Ld molecules by two-dimensional electrophoretic analysis of H-2Ld immunoprecipitates. These results indicate that the genomic clone 27.5 contains a functional BALB/c H-2Ld gene and demonstrate the usefulness of this approach for identifying the gene products encoded by cloned genes which are members of a multigene family. Furthermore, the ability to place cell-surface recognition molecules on the surfaces of foreign cells provides a powerful opportunity for functional analyses of these molecules. (Author abstract) (20 Refs)

69. EXPRESSION AND MODULATION OF VIRUS RECEPTORS ON LYMPHOID AND MYELOID CELLS: RELATIONSHIP TO INFECTIVITY.

Morishima T, McClintock PR, Billups LC, Notkins AL
(c/o Notkins) Lab. Oral Medicine, Natl. Inst. Dental Res., NIH, Bethesda, MD, 20205
Virology; 116(2):605-618 1982

Using a sensitive and specific assay for the binding of radiolabeled encephalomyocarditis (EMC) virus to cell surface receptors, we have measured the kinetics of virus attachment to murine lymphoid and myeloid cells, and have shown that receptors for this virus vary with the phase of cell growth and can be modulated or, in some cases, induced. The initial rate constant (KR) for resident peritoneal macrophages was 0.8 X 10(-9) cm3 min-1 cell-1, but after in vivo stimulation the rate of binding increased by a factor of 2. In contrast, unstimulated splenic T and B lymphocytes failed to bind EMC virus, but after exposure to appropriate mitogens, the initial rate constant increased to as high as 6.7 x 10(-9) cm3 min-1 cell-1. Studies with continuous cell lines showed that the binding of virus to receptors varied by up to 10-fold and was greatest during the exponential growth phase as compared to the stationary phase. Although the KR increased following exposure of lymphocytes to mitogens, immunofluorescence revealed that only a small fraction of the cells actually contained viral antigens, suggesting that virus receptors either were induced in only a small subpopulation of lymphocytes or that postattachment restriction prevented viral replication in a large fraction of the cells. A survey of six cloned BALC/c T and B cell lymphomas arrested at different stages of differentiation showed that two of these lymphomas possessed EMC virus receptors, arguing that receptors are present only at certain stages of cell differentiation. Evidence that receptors are functionally important comes from experiments which showed that only cells with a

KR greater than 0.1 x 10(-9) cm3 min-1 cell-1 are susceptible to infection. These studies suggest that factors which influence the expression and modulation of virus receptors may determine the outcome of certain viral infections. (36 Refs)

70. THE LATEST LABORATORY TESTS FOR CANCER.

Nichols WS, Nakamura RM
Dept. Pathology, Scripps Clinic and Res. Foundation, La Jolla, CA
Consultant; 21(6):131-134 1981

Screening procedures for cancer involving the use of tumor-associated antigens and endocrine-related, enzyme, virus-associated, and lymphocyte cell markers are described. The most useful tumor-associated antigens are those that have fetal components. Alpha-fetoprotein is an embryo-specific alpha-globulin that exists in healthy fetuses and in most persons with primary hepatic carcinoma. Elevated levels of carcinoembryonic antigen occur in many persons with colorectal cancer. Highest levels of pancreatic oncofetal antigen are found in patients with pancreatic carcinoma. Problems with specificity of tumor-associated antigens are discussed. Human chorionic gonadotropin assays are mainly used to monitor the progress of women who have been treated for hydatidiform mole or choriocarcinoma. An assay for pro-ACTH or ACTH may help distinguish between benign and malignant disease in patients with undiagnosed abnormalities that have been noted on x-ray films of the chest. A radioimmunoassay for calcitonin in the serum is useful in the diagnosis of medullary carcinoma of the thyroid. Plasma gastrin assay is a useful screening test for persons with severe peptic ulcer disease who are suspected of having Zollinger-Ellison syndrome. A thyroglobulin assay may be useful in the diagnosis of thyroid adenocarcinoma. Direct radioimmunoassay for serotonin in the serum or plasma is the test of choice for patients suspected of having carcinoid syndrome. 5-Hydroxyindoleacetic acid also may be used in the diagnosis of carcinoid syndromes. Estrogen receptor assays are useful in planning of therapy for breast cancer. (no Refs)

71. INTERFERON: IMMUNOBIOLOGY AND CLINICAL SIGNIFICANCE.

Stiehm ER, Kronenberg LH, Rosenblatt HM, Bryson Y, Merigan TC
Dept. Pediatrics, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Ann Intern Med; 96(1):80-93 1982

Interferons are proteins elaborated by infected cells that protect noninfected cells from viral infection. These proteins produce a temporary 'antiviral state' by altering nucleotide metabolism and cytoplasmic enzyme induction. Interferons appear early after viral infection locally and systematically to limit spread of viral infection; they also affect cell differentiation, growth, surface antigen expression, morphologic findings, and immunoregulation. Several human disorders have diminished interferon production. Newborns have normal interferon alpha but deficient interferon gamma production. Infants with congenital infections may also have defects in interferon production. Immunosuppressed patients receiving transplants (marrow, heart, or kidney) have diminished interferon production, particularly immediately after transplant. Deficiencies of interferon have also been noted in Down's syndrome, cellular immunodeficiencies, uremia, malnutrition, and hematopoietic malignancy. Leukocyte interferon has been of therapeutic value in herpes zoster infections, in patients with cancer, and in patients with hepatitis B infection. Interferon has not been proved to help children with congenital cytomegalovirus or rubella. Interferon can shrink lymphoid tumors, particularly non-Hodgkin's lymphoma. (Author abstract) (160 Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. STUDIES ON THE MATERNAL-INFANT TRANSMISSION OF THE HEPATITIS B VIRUS AND HBV INFECTION WITHIN FAMILIES.

Tong MJ, Thursby MW, Lin J-H, Weissman JY, McPeak CM
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:137-147 1981

Results of a study of hepatitis B virus (HBV) infection indicate that the major mode of infection in endemic areas may be

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maternal-infant transmission, although transmission may also occur by other modes. Many infants carrying hepatitis Bs antigen (HBsAg) develop anicteric CPH and become positive for hepatitis Be antigen. Intrafamilial clustering of HBV infection occurs in certain ethnic groups, regar dless of their location. Different infected members of a family may exhibit different clinical syndromes. Spread of HBV may be interrupted by treatment of infants of HBsAg mothers and careful use of HBV vaccine in HBsAg- family members. (11 Refs)

2. LOCALIZATION OF HEPATITIS B VIRUS ANTIGENS IN HEPATOCELLULAR CARCINOMA.

Nazarewicz-de Mezer T, Slusarczyk J, Krawczynski K, Nowoslawski A
Dept. Immunopathology, Natl. Inst. Hygiene, ul. Chocimska 24, 00-791 Warsaw, Poland
Prog Med Virol; 27:66-76 1981

Studies on the localization of hepatitis B (HBV) antigens by immunofluorescence or immunoperoxidase staining or by fluorochrome- or enzyme-labeled antibodies in cells of patients with hepatocellular carcinoma (HCC) are reviewed. All data obtained by immunomorphological analysis of HCC tissue and indicative of a decreasing potential of expression of HBV antigen with increasing malignancy are compatible with the hypothesis on the oncogenic properties of HBV. (50 Refs)

3. HEPATITIS B INFECTION AND PRIMARY LIVER CANCER.

Maupas P, Melnick JL
Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:1-5 1981

The statistical relationship between hepatitis B infection and primary liver cancer (PHC) is clear. Evidence from a recent workshop in Dakar, Senegal, is presented, including geographic distribution, endemiology, cirrhosis, DNA and antigen, and animal viral evidence. Hepatitis B vaccines and antibody induction treatment may contribute to a reduction in PHC, even though the precise etiologic relationship between the two diseases remains unknown. (no Refs)

4. HEPATOCELLULAR CANCER IN SOUTHERN AFRICAN BLACKS: HBEAG, ANTI-HBE, IGM-ANTI-HBC AND OTHER MARKERS OF HEPATITIS B.

Kew MC, Desmyter J, De Groote G, Frosner G, Roggendorf M, Deinhardt F
(c/o Desmyter) Rega Inst., Catholic Univ. Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium
Prog Med Virol; 27:41-48 1981

Using radioimmunoassay, frequency of HBeAg in 98 HBsAg-positive Southern African miners with hepatoma was similar to that in HBs-Ag-positive controls (13 vs 12%). Anti-HBe was slightly less prevalent in patients (60 vs 85%). Anti-HBs was much less prevalent, and anti-HBe and anti-HBc were more prevalent in 50 HBsAg-negative patients than in HBsAg-negative controls. HB markers were found in 88% of HBsAg-negative hepatoma cases and in 70% of HBsAg-negative controls; and in 96% of all hepatoma cases, vs 74% in the control population. All differences are significant. With a single exception, anti-HBe was found only in the presence of anti-HBc. IgM-anti-HBc was found much more frequently in HBsAg-positive patients than in the other groups. (Author abstract) (6 Refs)

5. HEPATITIS B INFECTION IN ALCOHOLIC LIVER DISEASE AND PRIMARY HEPATOCELLULAR CARC INOMA IN FRANCE.

Goudeau A, Maupas P, Dubois F, Coursaget P, Bougnoux P
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:26-34 1981

The prevalence of hepatitis B virus (HBV) markers was studied in 125 asymptomatic heavy drinkers, 163 patients with alcoholic cirrhosis, and 46 patients with histologically proven primary hepatocellular carcinoma. Hepatitis B surface antigen, anti-hepatitis B surface antigen, and anti-hepatitis B core antigen were tested by solid phase radioimmunoassay. Percentages of HBV markers in the three groups were, respectively, 31.2, 54.6, and 21.7, compared to 5% in a control group of 10,000 normal blood donors from the same area in France. (24 Refs)

6. DETECTION OF HEPATITIS B VIRUS ANTIGENS IN HEPATOCELLULAR CARCINOMA TISSUES.

Goudeau A, Maupas P, Coursaget P, Drucker J, Chiron JP, Denis F, Diop Mar I, N'Diaye PD
(c/o Maupas) Institut de Virologie, Facultes de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, F-37000 Tours, France
Prog Med Virol; 27:77-87 1981

A serological and pathological immunofluorescence study of hepatitis B (HBV) antigens was conducted on liver tissues obtained from 15 patients who died from primary hepatocellular carcinoma (PHC) in Dakar, Senegal, where PHC is obvious upon clinical examination and prevalent in patients in the 30-40 yr age range. Tissue localization of hepatitis B surface antigen and hepatitis B core antigen suggested the following etiological scheme for the HBV role in the genesis of PHC: hepatitis with inflammatory phenomena and necrosis followed by post-necrosis cirrhosis with fibrosis and voluminous regenerative nodules; and PHC evolving from the post-necrotic regenerative nodules. (20 Refs)

7. ATAXIA-TELANGIECTASIA: IMMUNOCYTOCHEMICAL DEMONSTRATION OF ALPHA-FETOPROTEIN AND HEPATITIS B SURFACE ANTIGEN IN THE LIVER.

Ohama E, Ikuta F
Dept. Neuropathology, Brain Res. Inst., Niigata Univ., Asahimachi 1, Niigata City, 951, Japan
Acta Neuropathol (Berl); 56(1):13-16 1982

The liver, thymus and associated tumor tissue (adenocarcinoma of the stomach in 3 patients and medulloblastoma of the cerebellum in 1 patient) from five autopsy patients with ataxia-telangiectasia (AT) was examined for alpha-fetoprotein (AFP) and hepatitis B surface antigen (HBsAg) using the peroxidase-antiperoxidase method. AFP and HBsAg was detected in the cytoplasm of hepatocytes from all five patients but was not detected in the thymus or tumor tissue. The presence of AFP is consistent with the suggestion that AT patients have an underdevelopment of the liver. More striking is the detection of HBsAg in the absence of clinical or histological evidence of acute hepatitis B virus (HBV) infection in these patients. It is possible that persistent infection with HBV may play a role in the etiology and pathogenesis of AT. AT may be unique among immunodeficiency diseases and HBV carriers in its association with both AFP and HBsAg in the liver. (17 Refs)

8. AFLATOXINS, B1, B2, G1, G2 IN PRIMARY LIVER CELL CARCINOMA.

Onyemelukwe GC, Ogbadu GH, Salifu A
Dept. Medicine, Ahmadu Bellow Univ., Zaria, Nigeria
Toxicol Lett; 10(2):309-312 1982

The presence or absence of circulating aflatoxins and other mycotoxins in adults (25-65 yr old) with primary liver cell carcinoma (PLCC) was investigated. Serum and urine samples were obtained from each of 20 and 7 PLCC patients, respectively. Serum aflatoxin levels were determined by Velasco Fluorotoxin meter. Mean serum aflatoxin, B1, B2, G1, and G2 levels were 0.069, 0.095, 0.083, and 0.040 ug/ml, respectively. Aflatoxin B1 levels greater than 0.15 ug/ml were measured in three patients; however, higher aflatoxin levels may have been present due to 24 hr serum clearance values of 0.025 to 0.050 ug/ml in these subjects. Hepatitis B surface antigen was detected in eight patients. Two other fungal metabolites, zearalenone, associated with cervical cancer in mice, and Phoma sorghina metabolite, associated with hemorrhagic thrombocytopenia, were identified in two separate urine specimens. Although evidence of aflatoxin carcinogenicity in man is inconclusive, foodstuffs should be protected from excessive aflatoxin contamination. (14 Refs)

9. NEW DEVELOPMENTS IN THE FIELD OF VIRUSES IN LIVER DISEASE.

Buffet C
Service d'hepatologie et de gastro-enterologie, hopital Bicetre, 78, rue du General-Leclerc, 94270 Kremlin-Bicetre, France
Rev Prat; 31(59):4251-4254 1981

Hepatitis A, the significance of hepatitis B virus (HBV) markers, HBV marker in alcoholics, HBV and carcinogenesis, and non-A, non-B (NANB) hepatitis virus are discussed. HBV antigens and antibodies (antibodies to HBV surface and core antigens and those related to viral replication) are discussed in relation to the diagnosis of hepatitis B. HBV markers are elevated in alcoholic populations (40%) as compared with normal blood donors (10%). In most alcoholics, HBV markers indicative of former, non-developing HBV infection are observed. The role of HBV in cirrhosis is discussed. Integration of HBV DNA in the cellular genome of hepatoma tissue has been demonstrated. Epidemiologically, geographic zones with a high incidence of hepatitis are strictly superimposable over zones with a high incidence of hepatomas. Patients positive for HBV antigens with or without cirrhosis show a higher incidence of liver neoplasms. Although other factors are involved in tumorigenesis in the liver, HBV is directly involved in the development of hepatomas. Identification, transmission, and characteristics of NANB hepatitis virus and re sultant infection are described. (13 Refs) (In FRE)

10. FREQUENCY AND TREATMENT OF PRIMARY HEPATOCELLULAR CARCINOMA IN LOS ANGELES.

Tong MJ, Chiebowski RT, Weissman JY, Bateman JR
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:6-13 1981

The majority (85%) of cases of primary hepatocellular carcinoma (PHC) in Los Angeles involved prior cirrhosis; alcoholism was a related factor in most cases of PHC reported from 1918 to 1973. Experience with 5-fluorouracil and adriamycin semustine chemotherapy indicated that successful treatment of PHC has not been found. Survival was longer in patients with serum bilirubin levels of less than 2 mg% than those with greater than 2 mg% and in patients who were negative for hepatitis B surface antigen than those who were positive. (25 Refs)

11. HEPATITIS B VIRAL MARKERS IN PATIENTS WITH CHRONIC HEPATITIS AND WITH PRIMARY HEPATOCELLULAR CARCINOMA IN TAIWAN.

Tong MJ, Chien MC, Lo KJ, Tsai YT, Lee JK
Liver Diagnostic Center, Huntington Memorial Hosp., 100 Congress St., Pasadena, CA, 91105
Prog Med Virol; 27:60-65 1981

Three prospective studies on the relationship between hepatitis B viral markers and primary hepatocellular carcinoma (PHC) were conducted with patients of Chinese origin at two veterans hospitals. The frequencies of hepatitis B surface antigen (HBsAg) and anti-HBs were determined in 94 chronic hepatitis patients, and the patients' progress was followed for 3 yr. Hepatitis B viral markers were measured by radioimmunoassay in a study involving 102 patients with PHC and HBsAg and anti-HBs were determined in patients with acute viral hepatitis (40), chronic hepatitis (161), and PHC (126). (6 Refs)

12. HEPATIC CANCER AND NON-A NON-B TYPE HEPATITIS.

Shibasaki K, Soga K, Honma A, Ichida F
Dept. Internal Medicine, Nippon Dental Coll. Niigata Dental Sch., Niigata, Japan
Nippon Rinsho; 39(10):3251-3256 1981

Patients with chronic hepatic disease included two groups according to presence or absence of hepatitis B surface (HBs) antigen. Hepatic cancer patients with continuous infection of hepatitis B virus (HBV) were classified B-type hepatocarcinoma, and those with non-A non-B (NANB)-type hepatitis were classified NANB type hepatic cancer. Characteristics of the groups were compared. HBs antigens were detected with the aid of RPHA method in 63/125 patients with chronic hepatitis, 33/129 with cirrhosis, and 57/114 with hepatic cancer. Examination of HBV related antigens and antibodies in the serum of 101 patients with hepatic cancer showed that 60/101 had continuous HBV infection, 31/101 had temporary HBV infection, and 10/101 had no detectable HBV antigens or antibodies. Studies of 129 patients with cirrhotic changes indicated that a higher rate of the patients with HBs antigens developed primary hepatic cancer than did those without HBs antigens. Other studies indicated that hepatic cancer occurred within a shorter period of time in patients with presence of HBs antigen than in those without HBs antigen. Comparison of characteristics of B-type hepatocarcinoma patients (B Group) and NANB-type hepatocarcinoma patients (NANB Group) showed that the B Group patients developed cancer with an average of 5 yr earlier than the NANB Group patients, the male:female ratio of the B Group was less than that of the NANB Group, more NANB Group patients had a history of blood transfusions and hepatitis, and more B Group patients had no history of alcohol consumption. (29 Refs) (In JPN)

13. CONFIRMATION OF HERPES SIMPLEX VIRUS TYPE 2 INFECTIONS IN HERPES-LIKE GENITAL LESIONS BY A SIMPLE COMPLEMENT-FIXATION TEST.

Arsenakis M, May JT
(c/o May) Dept. Microbiology, La Trobe Univ., Bundoora, Victoria 3083, Australia
Br J Vener Dis; 58(1):48-51 1982

A complement fixation test with a crude 4-hr herpes simplex virus (HSV)-2-infected human epidermoid carcinoma (HEP-2) cell extract, containing the immediate early HSV-2 antigen (AG-4), was used to distinguish rapidly between HSV-1 and HSV-2 infections. The test was also used to confirm clinically diagnosed genital herpes as HSV-2 infections. Blood samples were obtained from 64 patients (40 women, 24 men; 18-30 yr old) with genital herpes-like lesions and from 23 age- and sex-matched controls. The time-course appearance of complement-fixing antibody to AG-4 in recurrent HSV-2 and in primary HSV-1 and HSV-2 infection is presented. Over the 5-wk period, no anti-AG-4 complement-fixing antibody was detected in patients with HSV-1 infections. The antibody was usually detected 2 wk after a primary infection with HSV-2 and was still present 5 wk later. In 50% of patients with recurrent HSV-2 infections, the anti-AG-4 complement-fixing antibody was detected at 4 days and increased to a max titer at 2 wk after the lesions appeared. No more than 9% of the controls or patients with facial HSV-1 infections had positive results for the antibody. The results indicated that the complement-fixation test can confirm HSV-2 virus infection without isolation of the virus from the herpetic lesion. (13 Refs)

14. HERPES SIMPLEX VIRUS: CLINICAL SYNDROMES AND CURRENT THERAPY.

Rand KH
Div. Infectious Diseases, Univ. Florida, Box J-277 JHMHC, Gainesville, FL, 32610
Compr Ther; 8(2):44-50 1982

Herpes simplex virus (HSV) is discussed with respect to the primary infection, recurrent disease, latency, laboratory diagnosis, specific syndromes and their treatment, and its association with cancer. After the initial infection, HSV-1 or HSV-2, or both, persists for life in the sensory ganglia. Local recurrences occur on the skin yr after yr. Both HSV-1 and-2 have been shown to transform cultured cells and to cause cancer in animals. There is no reproducible, direct evidence that HSV-1 and-2 caused cancer in vivo, although HSV antigens and antibodies have been found in human tumors and patients with cancer. (14 Refs)

15. EPSTEIN-BARR VIRUS, CLINICAL SYMPTOMATOLOGY AND IMMUNODEFICIENCY IN NON-HODGKIN'S LYMPHOMA PATIENTS.

Fejes M, Mochanko K, Brezavscek D, Suarez A, Pavlovsky A, Bachmann AE
Departamento de Inmunohematologia, Instituto de Investigaciones, Hematologicas Academia Nacional de Medicina, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):137-140 1981

Incidence and levels of anti viral capsid antigen (anti-VCA) and anti Epstein-Barr nuclear antigen (anti-EBNA) antibody titers were studied in 62 patients with non-Hodgkin's lymphoma and in 52 healthy donors (HD). Rappaport histologic classification indicated that 20 of the patients had well differentiated lymphocytic lymphoma, 25 had poorly differentiated lymphoblastic lymphoma, and 17 had the histiocytic form of reticulosarcoma. The difference between values of anti-VCA and anti-EBNA in HD and in patients was not significant. No significant difference was noted when the anti-EBNA values were compared by histologic type; however, the anti-VCA geometric mean was lower in patients with lymphocytic or lymphoblastic lymphoma than in those with reticulosarcoma or in HD. Patients in remission had lower anti-VCA titers. No significant difference was observed between 29 immunodeficient patients and those found non-immunodeficient. (19 Refs)

16. COMPLEMENT-FIXING ANTIBODY TO EPSTEIN-BARR VIRUS SOLUBLE ANTIGEN IN POPULATIONS AT HIGH AND LOW RISK FOR NASOPHARYNGEAL CARCINOMA.

Levine PH, Ebbesen P, Connelly RR, Das S, Middleton M, Mestre M
NCI, Landow Bldg., ID-12, Bethesda, MD, 20205
Int J Cancer; 29(3):265-268 1982

Greenland Eskimos comprise an ethnic group with one of the highest recorded incidence rates for nasopharyngeal carcinoma in the world. Sera from 625 Eskimos and 73 Danes (Caucasians) living in Greenland, as well as from 62 Danes living in Denmark, were tested for complement-fixing antibody to Epstein-Barr virus (EBV) soluble antigen and, from this study group, 129 donors were matched by age and sex for a study comparing antibody to viral capsid antigen, early antigen, and soluble antigen. Both Eskimos and Danes living in Greenland had significantly higher titers of EBV antibodies than Danes living in Denmark, suggesting that environment was more important than genetics or socioeconomic factors in determining the antibody response to EBV. Age and sex were also factors, higher titers occurring in females and young Eskimos. (Author abstract) (21 Refs)

17. SYMPOSIUM ON TUMOURS IN THE TROPICS: HISTORICAL INTRODUCTION, BURKITT'S LYMPHOMA , NASOPHARYNGEAL CARCINOMA AND KAPOSI'S SARCOMA.

Hutt MS
Geographical Pathology Unit, Dept. Histopathology, St. Thomas' Hosp. Medical Sch., London SE1 7EH, England
Trans R Soc Trop Med Hyg; 75(6):761-765 1981

The geographic distribution of Burkitt's lymphoma (BL) in Africa and New Guinea can be explained by its association with endemic malaria. Heavy Plasmodium falciparum infection in young children suppresses the immune system and enhances lymphocyte proliferation, which in turn may enhance susceptibility to the oncogenic effects of the Epstein-Barr virus (EBV). The age at the time of EBV infection and genetically determined immunologic deficits may also be involved. The sporadic BL of Western nations is usually not associated with EBV. EBV is also implicated in nasopharyngeal carcinoma (NPC). Most of the high-NPC areas are in the tropics of Africa and Asia. Genetic factors seem to be involved. In Malaysia, Singapore, and Hong Kong, the NPC frequency is high in Malays and ethnic Chinese, but low in Indians. Chinese patients with NPC have a previously unidentified second-locus HLA antigen (Sin-2). The NPC frequency is also high among Eskimos, Aleuts, and Alaskan Indians. In this population, the BW40 component of the HLA system is more frequent in NPC patients than in other groups. Kaposi's sarcoma (KS) is rare everywhere in the world except among the black populations of tropical Africa. Its geographic distribution does not seem to be related to ethnic origin, suggesting that environmental factors are the major etiologic determinant. Endogenous, perhaps hormonal factors might account for the male preponderance

among KS patients. European and American cases of KS have been reported in immunosuppressed patients. An association of KS with elevated cytomegalovirus antibody titers has been reported in Western countries but not in Africa. (78 Refs)

18. THE CHINESE EPIDEMIOLOGICAL APPROACH OF NASOPHARYNGEAL CARCINOMA RESEARCH AND CONTROL.

De-The G
CNRS, Faculty of Medicine A. Carrel, Rue Guillaume Paradin, F. 69372 Lyon CEDEX 2, France
Yale J Biol Med; 54(1):33-39 1981

Nasopharyngeal carcinoma (NPC), the major cancer killer in Cantonese Chinese, represents one of the three cancer research priorities in China. Apart from some fundamental research projects on the Epstein-Barr virus (EBV), their main efforts are epidemiologically and clinically oriented. Major surveys in GuangDong and GuangXi provinces showed that high EBV/IgA/VCA serum levels can detect NPC at an early stage of the disease. Characterization of 'precancerous lesions' in the nasopharynx and among the EBV/IgA positive individuals is in progress in the Zangwu county of the GuangXi Autonomous Region. Preventive anti-viral intervention in these individuals is being discussed. Search for genetic and environmental chemi cal carcinogens is also carried out. This Chinese epidemiological approach complements well the fundamental Western studies on EBV and NPC. (Author abstract) (21 Refs)

19. THE AMERICAN BURKITT'S LYMPHOMA REGISTRY: EIGHT YEARS' EXPERIENCE.

Levine PH, Kamaraju LS, Connelly RR, Berard CW, Dorfman RF, Magrath I, Easton JM
Clinical Studies Section, Lab. Viral Carcinogenesis, NCI, Landow Building, Room 1D-12, Bethesda, MD, 20205
Cancer; 49(5):1016-1022 1982

Four hundred twenty-one Americans diagnosed as having Burkitt's lymphoma (BL), 409 from the United States, were studied by the American BL Registry to obtain information about the cause and control of this disease. Of these 421 cases, 256 were confirmed by our pathologists as being morphologically indistinguishable from African BL. A relationship between age and organ involvement was observed; cervical lymph nodes, ileum, and nasopharynx were initial sites of involvement primarily in younger patients. Although the Epstein-Barr virus (EBV) was less frequently associated with American BL than African, a high antibody titer to the EBV capsid antigen was associated with a more favorable prognosis. American BL resembled African BLs time-space clustering, male predominance, and excellent response to chemotherapy. Unlike African BL, however, more patients had involvement of cervical lymph nodes and bone marrow at an early stage of disease. American BL appears to be a more heterogenous disease than African BL. (Author abstract) (28 Refs)

20. LACK OF ASSOCIATION OF CYTOMEGALOVIRUS WITH ADENOCARCINOMA OF THE COLON.

Hart H, Neill WA, Norval M
(c/o Norval) Dept. Bacteriology, Univ. Edinburgh Medical Sch., Teviot Place, Edinburgh EH8 9AG, Scotland
Gut; 23(1):21-30 1982

Tumor specimens from patients with adenocarcinoma of the colon or rectum were examined for the presence of cytomegalovirus (CMV), and specimens of normal mucosa from the same patients were studied in parallel. Frozen sections of 14 specimens were made and the presence of CMV mRNA assayed by in situ hybridization using 3H-labeled CMV-DNA as a probe. Nine of these sections were also tested for cytomegalovirus antigens by immunofluorescence. No viral nucleic acids or antigens were detected. In addition to these direct approaches, the specimens were disaggregated and 19 were successfully cultured in various media over several months without yielding virus on any occasion. Areas containing epithelial cells were found in some cultures, foci of bipolar cells in others, while, in several, fibroblastic cells predominated. To ensure that any virus-containing cells were not lost by this method, the disaggregated tumor and normal intestinal cells were directly co-cultivated and also fused with human embryo lung cells, which are permissive for cytomegalovirus replication. The resulting cultures were examined over 2 to 3 mo for the presenc e of cytomegalovirus, and in no instance was virus found, despite attempted induction by iododeoxyuridine. Two fusion cultures became contaminated with cytomegalovirus, strain AD-169, which was being handled in the laboratory at the same time. The strain was identified by the pattern of viral DNA fragments produced by restriction endonuclease cleavage. Thus the accidental passage of virus in the heterokaryons did not alter its DNA and would further indicate the absence of any cytomegalovirus genomes in the adenocarcinoma cells. (Author abstract) (34 Refs)

21. AFLATOXIN LEVELS IN SERA OF HEALTHY FIRST TIME RURAL BLOOD DONORS: PRELIMINARY REPORT.

Onyemelukwe GC, Ogbadu G
Dept. Medicine, Ahmadu Bello Univ. Hosp., Zaria, Nigeria
Trans R Soc Trop Med Hyg; 75(6):780-782 1981

Serum levels of aflatoxin B1 (AB1), aflatoxin B2 (AB2), aflatoxin G1 (AG1), and aflatoxin G2 (AG2) were assayed in 20 first-time blood donors (25-40 yr old) and 15 sick persons (controls). The blood donors were all farmers from rural villages of the Guinea Savannah of Nigeria, cultivating and living on local staple foods (millet, sorghum, rice, and yams). The controls (including a man with nasopharyngeal carcinoma and a woman with hydatidiform mole) lived in villages near the hospital. Mean serum aflatoxin (AFL) levels in the blood donors were 0.123, 0.118, and 0.118 ug/ml for AB1, AB2, and AG1, respectively, and 0.064 ug/ml for AG2. Four blood donors showed AB1 levels of 0.2 ug/ml. Hepatitis B surface antigen (HBS-Ag) was present in the serum of 1/20 blood donors, who showed a low serum AFL level and no clinical disease. In the control group, serum AFL levels were significantly lower than in the farmers. The highest AFL levels (0.14 ug/ml of AB1, 0.24 ug/ml of AB2) were observed in the patient with nasopharyngeal cancer. Three patients with liver cirrhosis were positive for HBS-Ag and showed low serum AFL levels. Since liver function tests were normal in the farmers and in the absence of histological examination of their livers, it was difficult to speculate whether any of them had entered the multistage process of hepatic carcinogenesis. Further research is needed to evaluate the interactions (if any) between AFL and Epstein-Barr, hepatitis B, and cytomegaloviruses. (16 Refs)

22. COMPARATIVE LEUKEMIA: OF MICE AND MEN.

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Medicina (B Aires); 41(Suppl):199-206 1981

Results obtained using three experimental models testing for viral activity in human lymphoma over a 24-yr period are reviewed. Human lymphoma cells inoculated into mice indicated cross-immunity between lymphoma associated antigens. Sarcoma 180 intrasplenic inoculation into mice increased tu mor growth and metastases, an effect never observed with subcutaneous transplants; splenectomy increased tumor rejection. Human cells were obtained from biopsy of lymph node (LN), bone marrow (BM), or from in vitro lines of Burkitt, Epstein-Barr 1, Kudi, Jijoye, P3J, and the lymphosarcoma lines GH7 and LDLT. Controls were from normal human muscle (5 specimens), tonsils (6), and normal BM (4). After 10 days animals were killed, spleens homogenized and injected ip into 1-mo-old BALB/c mice, and the inoculated animals observed for 2 yr. Of the LN biopsy specimens from 93 patients with lymphoma, only 9 produced short term (10-43 days) leukemia; such results were reproducible 2 or 3 times in two cases and were not obtained in controls. Long latency leukemias (18 mo) were produced in 49% of animals. Experiments with AKR lymphoma cells gave similar results. Human lymphoblastoid cells injected into cylinders implanted in mice produced tumorigenesis in 62%, compared to 31% of animals implanted with normal lymphocytes and 45% with empty cylinders. The AKR cells in cylinders produced a 66% incidence of fibrosarcomas. When AKR cells or thymocytes were used as targets, antibodies were detected in sera from 66% of 118 acute lymphoid leukemia cases, 75% of 44 Hodgkin's lymphoma cases, and 0% of 171 normal blood donors; AKR lymphoma in mice produced similar results. The findings indicate that human lymphoma cells may behave like AKR lymphoma cells bearing antigenic determinants of Gross virus, which induces murine leukemia. (28 Refs)

23. DNA VIRUSES AND BRAIN TUMOURS.

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Trends Neurosci; 5(1):16-20 1982

Evidence for viral involvement in pathogenesis of some human neurogenic tumors is reviewed. In the case of neurogenic tumor models, direct injection of the virus into the brain eliminates the potential for the host to clear the virus by the immune system. However, certain viruses, such as JCV human papovavirus and adenovirus type 12, can be used to induce intracerebral neoplasms by host infection other than intracerebral injection. Some human viruses (ie human adenovirus type 12 and human papovavirus JCV) are oncogenic both in rodents and in higher primates, however reasons for the differences in oncogenic potential between the various adenovirus serotypes is not known. Locations of the intracellular virus in DNA sequences have not been clearly defined, although some studies indicate that certain viral genes are only found at a limited number of sites; gene cloning techniques should help to evaluate the cellular sites of viral integration and their functions. Other studies suggest that viral genes are essentially fixed in the DNA sequence in virus-induced tumors. However, integrated viral genomes may be lost from transfo rmed cells under certain circumstances. Presence of virus-specific RNA in virus-induced tumor cells is demonstrated by the presence of the so-called tumor(T)-antigen. Etiology of human neurogenic neoplasms is not clear, and proof of a viral etiology of human tumors must largely be circumstantial, yet there are observations that may point to tumor-virus involvement (eg adenovirus) in the pathogenesis of human neurogenic neoplasms. (15 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

24. EFFECT OF METHYLATION ON EXPRESSION OF MICROINJECTED GENES.

Waechter DE, Baserga R
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Proc Natl Acad Sci USA; 79(4,part1):1106-1110 1982

The cloned genes for the simian virus 40 large tumor antigen and for herpes simplex virus (HSV) thymidine kinase (TK) were methylated with EcoRI methylase. The genes were microinjected into the nuclei of TK-deficient (tk-) cells, and expression of the genes was determined by immunofluorescence staining for the simian virus 40 large tumor antigen and by [3H]thymidine incorporation followed by autoradiography for HSV TK. We found that methylation of the simian virus 40 gene, under EcoRI or EcoRI* conditions, resulting in methylation at sites within the gene and in the surrounding sequences, has no effect on expression of the large tumor antigen when the gene is manually microinjected into mammalian nuclei. However, methylation of the HSV tk gene at the two EcoRI sites markedly reduces or abolishes the expression of this gene. Of the EcoRI sites of HSV tk is approx 1.1 kilobases downstream from the 3' end of the gene and is believed to have no regulatory function in the expression of the tk gene. The other EcoRI site is 79 base pairs upstream from the 5' end of the gene and has considerable homology to the regulatory sequence proposed by Benoist, O'Hare, Breathnach, and Chambon. Our results are direct proof that methylation can alter gene expression and also that the effect depends strictly on the sites that are methylated. (Author abstract) (40 Refs)

25. SIMIAN VIRUS 40 MUTANT WITH TRANSPOSED T-ANTIGEN AND VP1 GENES.

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Dept. Molecular Biology and Genetics, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
J Virol; 41(3):1025-1037 1982

A simian virus 40 mutant with T-antigen gene transposed to the late region or the viral genome has been constructed. This transposed molecule directed the synthesis of a full-sized, 92,000-dalton large T antigen in both permissive and nonpermissive cells. This large T antigen functioned in the initiation of viral DNA replication and in the transformation of nonpermissive cells. T-antigen synthesis by this transposed genome had the characteristics of late transcription, thus indicating that functional large T antigen of simian virus 40 is not required for the initiation of late transcription. (Author abstract) (62 Refs)

26. UNCOUPLING OF SV40 TSA REPLICON ACTIVATION FROM DNA CHAIN ELONGATION BY TEMPERATURE SHIFTS AND APHIDICOLIN ARREST.

Dinter-Gottlieb G, Kaufmann G
Biochemistry Dept., Weizmann Inst. Science, Rehovot 76100, Israel
Nucleic Acids Res; 10(2):763-773 1982

To synchronize SV40 replicons, simian cells infected with a tsA mutant were restricted at 40 C, to complete ongoing replication and returned to 32 C, to activate new replicons in the presence of the DNA chain elongation inhibitor aphidicolin. Upon further incubation at 40 C without the drug, 3H-dT was incorporated into SV40 FI DNA, almost to the extent seen with cells recovered in the absence of the drug. To determine whether DNA synthesis would begin from the origin, following the temperature-shifts-aphidicolin regimen, chains subsequently pulse-labeled with (alpha-32P)dGTP in isolated nuclei were analyzed for size distribution and genomic location. These chains reached up to 300-400 nucleotides in size, unlike the control which featured comparable amounts of label in long chains and Okazaki pieces. The nascent DNA of the drug-treated system could be chased into longer chains, indicating that it was a replicative intermediate; and it hybridized preferentially to an origin proximal fragment of AtuI-restricted SV40 DNA, demonstrating partial replicon synchronization. The data prove that T-antigen activates the SV40 replicon independent of DNA chain elongation and suggest means to study the mechanism of DNA chain priming at the origin. (Author abstract) (30 Refs)

27. SMALL T PROTEIN OF SIMIAN VIRUS 40 IS REQUIRED FOR DENSE FOCUS FORMATION IN A RAT CELL LINE.

Sugano S, Yamaguchi N, Shimojo H
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J Virol; 41(3):1073-1075 1982

Incomplete foci were formed in a Fischer rat cell line infected with simian virus 40 deletion mutants encoding defective small t antigen. The foci were small and rarely piled up. The fraction of DNA-synthesizing cells in the foci was about half of that induced by wild-type virus. (Author abstract) (9 Refs)

28. DETECTION OF SIMIAN VIRUS 40 SURFACE-ASSOCIATED LARGE TUMOR ANTIGEN BY ENZYME-CATALYZED RADIOIODINATION.

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Int J Cancer; 29(3):337-344 1982

To facilitate detection of SV40 surface-associated tumor antigen (T-ag), conditions were established to surface label T-ag on intact cells by lactoperoxidase-catalyzed radioiodination (125I/LPO). SDS-PAGE analysis of anti-T immunoprecipitates of SV40-transformed and -infected cells labeled with 125I/LPO revealed the presence of iodinated T-ag. Several types of control experiments were employed t o guarantee the surface specificity of the 125I/LPO labeling technique. When SV40-transformed mouse cells were surface labeled with lactoperoxidase and glucose oxidase immobilized on insoluble beads, a preparation less readily internalized than soluble enzymes, T-ag was iodinated. Selective immunoprecipitation of surface antigens demonstrated that lactoperoxidase did not iodinate internally localized T-ag. A reconstruction experiment in which an extract of SV40-infected cells was added to uninfected cells prior to surface labeling suggested that T-ag released from lysed cells did not adhere significantly to monolayer surfaces and become iodinated. Finally, systematic omission of reactants from the iodination reaction revealed that exogenous addition of lactoperoxidase and H2O2 was necessary to generate an iodinated T-ag, indicating that endogenous host cell reactants do not contribute significantly to the iodination of T-ag. 125I-labeled T-ag was detectable on the surface of SV40 tsA-infected cells as the nonpermissive temperature 24 hr postinfection, indicating that the tsA lesion does not prevent the interaction of T-ag with the cell surface. When 125I/LPO-labeled transformed or infected cells were chased for 2.5 hr after labelling, iodinated T-ag was no longer associated with the cell monolayer but was immunoprecipitable from culture supernatants. Cultures from which labeled T-ag had been shed could then be relabeled with 125I/LPO and surface-associated T-ag was again detectable. These data suggest that surface-associated T-ag is continuously shed from the cell surface and is rapidly replaced in the membrane by intracellular T-ag. (Author abstract) (62 Refs)

29. SIMIAN VIRUS 40 LARGE TUMOR ANTIGEN: A 'RNA BINDING PROTEIN'?

Khandjian EW, Loche M, Darlix JL, Cramer R, Turler H, Weil R
Dept. Molecular Biology, Univ. Geneva, 1211 Geneva, Switzerland
Proc Natl Acad Sci USA; 79(4,part1):1139-1143 1982

Simian virus 40 large tumor antigen was isolated by immunoaffinity chromatography from monkey or mouse cell cultures undergoing lytic or transforming infection. RNase-treated gel-purified large tumor antigen, on hydrolysis with alkali, gave about equimolar amounts of AMP, CMP, and UMP. Furthermore, RNA fragments of approx 45 nucleotides could be isolated from large tumor antigen purified by the same procedure. Mapping of the T1 oligonucleotides showed a high complexity, as indicated by the presence of unique sequences of 15-30 nucleotides and of poly(A). This is compatible with the hypothesis that these RNA fragments are derived from cellular pre-mRNAs or mRNAs. Our results suggest that Simian virus 40 large tumor antigen is a RNA-binding protein and might possibly be involved in regulation of synthesis, maturation, or translation of cellular mRNAs. (Author abstract) (39 Refs)

30. ALTERATIONS IN MICROFILAMENTOUS AND MICROTUBULAR STRUCTURES ACCOMPANIED BY CELL GROWTH OF SV40-TRANSFORMED CLONAL MACROPHAGES, LINE 28-12 AND ITS SUBLINE.

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Cell Struct Funct; 6(4):329-339 1981

Morphological patterns of sets of actively growing and stationary simian virus 40 (SV40)-transformed macrophages of the clonal line 28-12, obtained from SV40-infected cultures of mouse bone marrow cells, were compared with those of the slowly growing subline 28-12(Ara) isolated from cytosine arabinoside-treated cultures. Transmission and scanning electron microscopic observations revealed microfilamentous and microtubular structures in the cells. Bundles of 70 A microfilaments were found in fully-transformed, actively growing 28-12 cells but not in minimally-transformed, stationary 28-12 cells, an observation which inconsistent with other studies. A decrease in microtubules apparently occurs in actively growing cells which have high levels of SV40 T-antigen, although evidence is not unequivocal. Response of the cells to colchicine

shows that cytoskeletal structures, including microtubules, are affected by transformation. The 28-12(Ara) cells, which are considered moderately transformed cells, have a significant amount of SV40 T antigen, fewer microtubules than either type of 28-12 cells, lower response to colchicine, and slower growth, but the cells also have a phagocytic capacity. (32 Refs)

31. SPECIES- AND GENUS-SPECIFIC ANTIGENIC DETERMINANTS OF SIMIAN AGENT 12 VP1 AS DEFINED WITH MONOCLONAL ANTIBODIES.

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Virology; 117(2):490-495 1982

Monoclonal antibodies were developed against the baboon papovavirus simian agent 12 (SA12). Both SA12-specific and simian virus 40-polyoma Papovaviridae genus-reactive monoclones were isolated. Immunoprecipitation and SDS-PAGE of [35S]methionine-labeled SA12 revealed that all monoclonal antibodies, whether SA12 specific or reactive throughout the genus, were directed against the major capsid protein, VP1, thus directly confirming antigenic polymorphism in this polypeptide. (Author abstract) (24 Refs)

32. PROPAGATION OF HUMAN HEPATITIS A VIRUS IN CELL LINES OF PRIMARY HUMAN HEPATOCELLULAR CARCINOMAS.

Deinhardt F, Scheid R, Gauss-Muller V, Frosner G, Siegl G

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Prog Med Virol; 27:109-113 1981

Successful infection of the hepatoma PLC/PRF/5 cell line with hepatitis A virus (HAV) and detection of HAAg and HBsAg antigens by radioimmunoassay and immunofluorescence are described. HAV also multiplied in HEP 3 B 2.17 cells but could not be grown in HBV-negative Malavu cells. HAV has uncharacteristically slow growth for a supposed enterovirus and has other unique characteristics which may make comme rcial vaccine production difficult. (11 Refs)

33. HEPATITIS B VIRUS SURFACE ANTIGEN PRODUCTION IN ESCHERICHIA COLI.

Charnay P, Gervais M, Louise A, Galibert F, Tiollais P

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Prog Med Virol; 27:88-92 1981

A derivative of bacteriophage lambda was prepared which carried a fusion between the beta-galactosidase (BG) gene (lacZ) and the hepatitis B surface antigen (HBsAg) coding sequence (lambdalacHBs-1). Infection of Escherichia coli with lambdalacHBs-1 leads to biosynthesis of a polypeptide of 138,000 mol wt, the expected size of the fusion polypeptide, which has antigenic determinants of both BG and HBsAg. This model of coupling HBsAg with a carrier protein in immunoreactive form may ultimately be useful in vaccines against hepatitis B virus infection. (24 Refs)

34. LARGE-SCALE PRODUCTION OF HEPATITIS B VACCINE.

Funakoshi S, Ohmura T, Fujiwara T, Suyama T, Naito R

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Prog Med Virol; 27:163-167 1981

Preparation of Hepatitis B vaccine according to the Maupas purification method is reported. More than 4 mg of purified hepatitis B surface antigen can be produced from 1 liter of plasma. One batch consists of 20,000-50,000 vials, although the facilities have the capacity to produce more than 10x that much. The first lot was prepared and gave satisfactory results in the gel diffusion test, polypeptide analysis, electron microscopy, inactivation test with chimpanzees, and a guinea pig potency test. (2 Refs)

35. SELECTION OF MOUSE CELLS PRODUCING HEPATITIS B SURFACE ANTIGEN AFTER TRANSFORMATION WITH CLONED VIRAL DNA.

Pourcel C, Dubois MF, Rousset S, Chany C, Tiollais P

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Prog Med Virol; 27:93-98 1981

Using cotransformation of Ltk- mouse fibroblasts with two plasmids bearing, respectively, two cloned Eco hepatitis B virus (HBV) DNA in tandem head to tail and cloned herpes virus (HSV) tk gene, mouse cell lines were selected which could synthesize hepatitis B surface antigen (HBsAg). All the Ltk selected clones synthesized HBsAg, indicating that they had received two plasmids. HBV DNA was integrated into high mol wt cellular DNA, and the original tandem structure was conserved. HBsAg synthesis in mouse cells showed that human viral gene transcription and translation was possible in the cells. (13 Refs)

36. RAPID SEROLOGICAL TECHNIQUE FOR TYPING HERPES SIMPLEX VIRUSES.

Cleveland PH, Richman DD, Oxman MN, Worthen DM

Res. Service, Veterans Administration Medical Center, Univ. California, San Dieg o, CA, 92161

J Clin Microbiol; 15(3):402-407 1982

A rapid serological technique for typing herpes simplex viruses (HSV) is described. The sensitive 125I-labeled staphylococcal protein immunoassay in which viral antigenes are nonspecifically immobilized on filter paper disks in an immunofiltration manifold was adapted to the typing of HSV isolates. The sensitivity of the technique permits the assay to be carried out with a small number of infected cells and to be performed directly with the primary isolate. (28 Refs)

37. MALIGNANT TRANSFORMATION OF CELLS OF NEWBORN HAMSTERS BY HERPES SIMPLEX VIRUS TYPE 2.

Kitsak VIa

Central Inst. Advanced Training for Physicians, Moscow, USSR

Vopr Virusol; (6):750-753 1981

Malignant transformation induced by herpes simplex virus Type 2 (HSV-2) was studied in cultured fibroblasts from 3-5 day old hamsters. Infection of primary culture with UV-inactivated HSV-2 caused morphological transformation of cells; first signs of morphological transformation were detected 14-25

days after infection. Characteristic features of morphological transformation were the loss of contact inhibition, multilayer growth, and progressive replacement of epithelioid cells by fibroblastlike cells. Immunofluorescent analysis showed the presence of virus-specific antigen in 5-30% of transformed cells, but transformed cells did not produce the infectious virus. Syngeneic newborn hamsters inoculated sc with transformed cells developed fibrosarcomas. Duration of the latent period was correlated with the number of passages in vitro (from 12 wk after 27 passages to 4 wk after 50 passages). (11 Refs) (In RUS)

38. MUTATION CAUSING PREMATURE TERMINATION OF THE POLYOMA VIRUS MEDIUM T ANTIGEN BLOCKS CELL TRANSFORMATION.

Templeton D, Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Virol; 41(3):1014-1024 1982

We used site-specific mutagenesis to introduce a termination codon, TGA, into the reading frame for the polyoma virus medium T antigen. We induced this mutation in a region of the polyoma genome in which the overlapping coding regions for the large and medium T antigens are translated in different reading frames. Therefore, the mutation terminated translation of the medium T antigen, but it caused only a single amino acid substitution in the large T antigen and did not affect the small T antigen. Cells infected by the mutant virus produced normal-size small and large T antigens. The infected cells produced a 28,000-dalton fragment of the 48,000-dalton medium T antigen, whose size and tryptic peptide map were consistent with its being a truncated N-terminal fragment terminating at the new termination codon of the mutant. Immunoprecipitates of mutant-infected cell extracts did not show medium-T-antigen-associated protein kinase activity. The mutant virus replicated normally in mouse 3T6 cells and induced cellular DNA synthesis in resting mouse 3T3 cells, but it failed to transform rat or hamster cells, as judged by focus formation and growth in agar. The mutant complemented a tsA mutant which affects the large T antigen for transformation, implying that the mutant defect for transformation was in the medium T antigen. These results imply that the small T antigen and the large T antigen together are insufficient to cause transformation and support the conclusion that the medium T antigen is essential for cell transformation by polyoma virus. (Author abstract) (31 Refs)

39. COMPARISON OF THE POLYOMA VIRUS EARLY AND LATE PROMOTERS BY TRANSCRIPTION IN VIVO.

Jat P, Cowie A, Kamen R
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Nucleic Acids Res; 10(3):871-887 1982

Polyoma virus DNA was transcribed in the HeLa whole cell extract in vitro system. Early region transcripts with the same 5'-ends as in vivo mRNAs, located 31 -2 bp from 'TATA'-boxes, were synthesized by RNA polymerase II. Sequences sufficient for efficient expression of the early promoter were present in a substitution mutant lacking viral DNA from a position 55bp before the principal cap sites. Late region transcripts were synthesized inefficiently. Only one (at nt5129 -2) of the many late mRNA cap sites functioned as an in vitro initiation point. This was the one 5'-end located 31 -2 bp from a sequence resembling the 'TATA' consensus. The proportion of late to early region RNA polymerase II transcripts decreased dramatically at suboptimal template concentrations. An hypothesis to explain the regulation of late gene expression in vivo based on these results is proposed. Although linear templates were transcribed only by RNA polymerase II, transcripts with the same sense as late mRNAs and 5'-ends at nt5076 -2 were produced from superhelical templates by an alpha-amanitin resistant enzyme. (Author abstract) (52 Refs)

40. STABILITY OF POLYOMA DNA SEQUENCES AND VIRUS-CODED PROTEINS DURING TUMOR FORMATION.

Chowdhury K, Meltzer ML, Israel MA
Lab. Molecular Microbiology, Natl. Inst. Allergy and Infectious Disease, NIH, Bethesda, MD, 20205
J Virol; 41(3):1000-1006 1982

To determine the stability of polyoma viral DNA in transformed rat cells during their growth in vivo, we compared the state and arrangement of polyoma virus DNA sequences in virus-transformed rat cell lines before and after their passage in vivo. In cell lines from 12 independent tumors induced by the inoculation of animals with three different transformed cell lines, we could detect no significant changes in the arrangement of viral DNA sequences associated with the in vivo passage of these cell lines. In 13 of 14 tumor cell lines examined, the pattern of polyoma virus tumor antigens, characterized by the presence of the polyoma virus large, middle, and small tumor antigens, was unchanged. (Author abstract) (23 Refs)

41. MONOCLONAL ANTIBODIES AGAINST POLYOMA VIRUS TUMOR ANTIGENS.

Dilworth SM, Griffin BE
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Proc Natl Acad Sci USA; 79(4,part1):1059-1063 1982

A method is described for the production of hybridoma cell lines secreting antibodies directed against the polyoma virus tumor antigens (T-Ags). Ten cloned lines have been established by this procedure and designated alphaPy Cl and C4, with activities against all three T-Ags; alphaPy LT1,-4, and-7, with activities against large T-Ag only; and alphaPy MT5,-7,-10,-13, and-16, with activities against middle T-Ag only. Some of the antibodies appear to react also with specific cellular proteins. Data from studies on alphaPy MT7 point to the possible existence of more than one antigenic form of the viral middle T-Ag and, similarly, from studies on alphaPy LT7, to more than one form of large T-Ag. The approx positions on the polyoma virus genome of the sequences encoding antigenic determinants have been mapped by using defined polyoma virus deletion mutants. The availability of these monoclonal antibodies allows the isolation of large amounts of viral T-Ags. (Author abstract) (30 Refs)

42. AN IMMUNOPEROXIDASE STUDY OF CYTOMEGALOVIRUS MONONUCLEOSIS.

Abramowitz A, Livni N, Morag A, Ravid Z
Dept. Pediatrics, Hadassah-Hebrew Univ. Medical Center, P.O. Box 12,000, Jerusalem, Israel
Arch Pathol Lab Med; 106(3):115-118 1982

Indirect immunoperoxidase method was used to evaluate retrospectively a case of cytomegalovirus (CMV) mononucleosis. Specific rabbit antiserum against CMV was used as primary reagent in routinely prepared paraffin sections of lymph node and in fixed slide preparations of the bone marrow aspirate. Staining specific for CMV antigen was observed in the lymphoid cells of the lymph node in the predominantly T-cell

area and in the large lymphoid cells of the bone marrow. Bone marrow lymphoid cells with morphologic characteristics similar to those of the cells positive for CMV antigen showed positive immunoperoxidase reaction with specific rabbit antihuman T-cell serum. The data strongly indicate that CMV antigen was localized predominantly in the cells of lymphoid origin during the acute stage of the CMV mononucleosis; some data also suggest that infected lymphoid cells may be of T-cell origin. An immunoperoxidase technique is advantageous in both diagnosing and evaluating CMV mononucleosis. (Author abstract) (24 Refs)

43. EPSTEIN-BARR VIRUS (EBV) RECEPTOR IMPLANTATION ONTO HUMAN B LYMPHOCYTES CHANGES IMMUNOGLOBULIN SECRETION PATTERNS INDUCED BY EBV INFECTION.

Tsukuda K, Volsky DJ, Shapiro IM, Klein G
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden
Eur J Immunol; 12(1):87-90 1982

Mosaic membrane vesicles containing both Epstein-Barr virus (EBV) receptors and Sendai virus envelope proteins were allowed to form by the previously described membrane solubilization and co-reconstitution technique. The vesicles were allowed to fuse with the membranes of normal human B lymphocytes, whereafter the cells were infected with transforming EBV (B95-8 substrain). Compared to similarly infected but otherwise unmanipulated cells, the receptor-implanted lymphocytes responded with a larger number of EBV-determined nuclear antigen positive and immunoglobulin-secreting plaque-forming cells (PFC). Moreover, there was a clear increase of the IgG/IgM PFC ratio in the receptor-implanted B lymphocytes. These results show that not all human B lymphocytes that can potentially be activated by EBV express functional EBV receptors. B lymphocytes programmed to secrete IgG appear to be more defective in this respect than IgM secretors. (Author abstract) (27 Refs)

44. ANTIVIRAL SPECIFICITIES OF IMMUNOGLOBULINS SECRETED BY HUMAN LYMPHOCYTES IMMORTALIZED IN VITRO WITH EPSTEIN-BARR VIRUS.

Seigneurin JM, Desgranges C, Renversez JC, Baccard M, Micouin C
Laboratoire de Virologie, Centre Hospitalier Universitaire, Grenoble, France
Ann Virol; 132(3):323-335 1981

Human B lymphocytes from a chronic T-lymphocytic leukemia patient were immortalized through the use of two Epstein-Barr (EBV) strains, both obtained after passage in marmoset lymphocytes, Ma-B95-8 from an infectious mononucleosis patient, and Ma-M81 from lymphocytes invading the tumor of a nasopharyngeal carcinoma patient. Features of the two established cell lines are described especially in relation to polyclonal synthesis of virus specific antibodies. Characteristics of the patient's lymphocytes are described. The two cell lines established were clearly of B-cell origin. Both cell lines contained Epstein-Barr nuclear antigen in 100% of the cells. EBV early antigen was evident in 1.8% of Ma-B95 cells and 3.0% of Ma-M81 cells. EBV viral capsid antigen was found only in 3.0% of Ma-M81 cells. Both lines expressed complement 3 and EBV receptors and surface-bound immunoglobulin. Ultrastructurally, Ma-M81 had the typical features of a lymphoblastoid cell line, while Ma-B95 had features of plasmacytoid cells. Ma-B95 cells secreted a high level of immunoglobulins (32 ug/10(6) cells), including 24 ug IgG, while Ma-M81 cells produced only 3.8 ug. At the time the cell lines were established, the patient possessed antiviral antibodies against several viruses, cytomegalovirus, respiratory syncytial virus, and measles virus, which were found in the immunoglobulin secreted by Ma-B95. The Ma-M81 cell line produced complete EBV virion, while in the Ma-B95 cells the replicative cycle of EBV was blocked at the early antigen stage. (39 Refs)

45. ESTABLISHMENT AND CHARACTERIZATION OF AN EPSTEIN-BARR VIRUS-NEGATIVE LYMPHOMA B-CELL LINE FROM A PATIENT WITH A DIFFUSE LARGE CELL LYMPHOMA.

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Cancer Res; 42(4):1368-1373 1982

Cell line (LNPL) was established from a tumor biopsy of a nasopharyngeal 'histiocytic' lymphoma composed of large noncleaved B-cells. LNPL expressed immunoglobulin M kappa surface immunoglobulin, as did the original tumor. LNPL also expressed Ia antigen but lacked Epstein-Barr virus nuclear antigen. It exhibited a translocation between chromosomes 8 and 14 which has been described in certain other malignant lymphoproliferative disorders. An autologous T-cell line lacked the translocation between chromosomes 8 and 14. LNPL is being used as an immunogen to produce monoclonal antibodies in our laboratory. Such cell lines may facilitate identification of lymphoma-associated surface antigens. (Author abstract) (36 Refs)

46. ADENOVIRUS E1B-58KD TUMOR ANTIGEN AND SV40 LARGE TUMOR ANTIGEN ARE PHYSICALLY ASSOCIATED WITH THE SAME 54 KD CELLULAR PROTEIN IN TRANSFORMED CELLS.

Sarnow P, Ho YS, Williams J, Levine AJ
State Univ. New York, Stony Brook, NY, 11794
Cell; 28(2):387-394 1982

The adenovirus E1b-58kd tumor antigen has been detected in a physical association with a 54 kilodalton cellular protein in adenovirus-transformed mouse cells. Antibody specific for the E1b-58kd protein coimmunoprecipitates a 54 kd protein from transformed, but not from productively infected, cells. Monoclonal antibody specific for the cellular 54 kd protein coimmunoprecipitates the adenovirus E1b-58kd protein from transformed cell extracts. The same or closely related cellular 54 kd protein, associated with the adenovirus E1b-58kd protein, was present in the SV40 large T antigen-54 kd complex previously detected in SV40-transformed mouse cells. The identity of the 54 kd protein is based on the immunological specificities of the anti-54 kd monoclonal antibodies and partial peptide maps of the 54 kd protein associated with the adenovirus and SV40 tumor antigens. The adenovirus E1b-58kd-54 kd complex, like the SV40 large T antigen-54 kd complex, is heterogeneous in size or mass. While all of the cellular 54 kd protein in the adenovirus-transformed cell extract is found in a complex with the E1b-58kd protein, some of the viral 58 kd antigen is detected in a form not associated with the 54 kd protein. The fact that the adenovirus and SV40 tumor antigens, both required for transformation, can be found in physical association with the same cellular protein in a transformed cell is a good indication that these two diverse viral proteins share some common mechanisms or functions. (Author abstract) (43 Refs)

47. A DEFICIENCY IN THE REPAIR OF UV AND GAMMA-RAY DAMAGED DNA IN FIBROBLASTS FROM COCKAYNE'S SYNDROME.

Rainbow AJ, Howes M

Dept. Radiology, McMaster Univ., Hamilton, Ontario L8S 4J9, Canada

Mutat Res; 93(1):235-247 1982

DNA-repair deficiencies were investigated in fibroblasts from five unrelated patients with Cockayne's syndrome (CS) and two patients heterozygous for CS. Suspensions of adenovirus type 2 were exposed to UV or gamma irradiation. Fibroblasts were then infected with irradiated or nonirradiated virus and then incubated. The fibroblasts were then assayed by immunofluorescence methods for expression of viral structural antigens. Results obtained from CS fibroblasts were compared with results obtained from normal and xeroderma pigmentosum (XP) fibroblasts. Host-cell reactivation (HCR) of viral function for both UV- and gamma-irradiated virus was reduced in homozygous CS fibroblasts. The dose of UV required to reduce viral function in homozygous CS fibroblasts by 37% (D37) was 14-35% of the D37 for normal cells. D37 for gamma-irradiation of CS cells was 61-80% of that for normal cells. One heterozygous CS strain had a D37 for UV-irradiated virus 68% of normal, intermediate between the D37 for homozygous CS and normal cells. The other heterozygous CS strain had a normal D37. Results indicate that CS fibroblasts have a defect in DNA repair mechanisms. (41 Refs)

48. CHARACTERIZATION OF HEAVY PARTICLES OF ADENO-ASSOCIATED VIRUS TYPE 1.

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J Gen Virol; 58(part1):63-72 1982

The temperature-sensitive mutant ts4 of adenovirus type 2 (Ad-2) is capable of complementing adeno-associated virus type 1 (AAV-1) in HEp2, KB and HEK cells at 34 C and 39 C when used as a helper virus. Heavy non-infectious AAV-1 particles can be generated by using the mutant ts4 in HEp2 cells. When AAV-1 is grown in serial passages in HEp2 cells, both the wild-type Ad-2 and the mutant ts4 give rise to heavy, less infectious AAV-1 particles. The heavy AAV-1 particles generated by Ad-2 in advanced serial passages retain the property of having CF and IF antigens, but the AAV-1 generated by the mutant in advanced serial passages lose this property. There is no appreciable difference in the particle counts made by electron microscopy of AAV-1 preparations generated either by Ad-2 or the mutant ts4. Analysis by polyacrylamide gel electrophoresis of purified heavy AAV generated by ts4 indicates that in late passage an additional polypeptide of higher mol wt than the three structural polypeptides is detected. (Author abstract) (37 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

49. EXPRESSION OF ENDOGENOUS RETROVIRAL GLYCOPROTEIN 70 BY ANTIGEN-ACTIVATED CYTOTOX IC AND SUPPRESSOR T LYMPHOCYTES OF MICE.

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Proc Natl Acad Sci USA; 79(4,part1):1250-1253 1982

Concanavalin A-stimulated murine spleen cells and antigen-stimulated B lymphocytes of normal mice express an antigen that reacts with goat antiserum against glycoprotein (gp) 70. Structural analysis of this antigen characterizes it as endogenous virus gp70 that is most likely of xenotropic origin. Activated nonspecific T suppressor cells and cytotoxic T lymphocytes express endogenous viral gp70, whereas nonactivated mouse T or B lymphocytes do not. The presence of endogenous retroviral gp70 is thus a novel marker for activated mouse lymphocytes in general. (Author abstract) (37 Refs)

50. CHARACTERIZATION OF XENOTROPIC AND DUAL-TROPIC TYPE C RETROVIRUSES ISOLATED FROM ABELSON TUMOUR.

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J Gen Virol; 58(part1):115-125 1982

Tumors induced in Balb/c mice by Abelson virus complex were found to contain a xenotropic virus (A-X-MuLV) and an NB-tropic, dual-tropic virus (NBX), in addition to the Moloney leukemia virus (M-MuLV) and the defective, transforming Abelson virus genome. Both A-X-MuLV and NBX virus were presumably present in a genomically masked form and could be recovered only by co-cultivation of tumor cells with permissive cells. Only about 0.87% and 0.13% of the viruses in the co-culture supernatant represented A-X-MuLV and NBX virus respectively; the majority were M-MuLV. The NBX virus acted more efficiently than the HIX virus as helper to rescue murine sarcoma virus (MSV) from SL- cells of hamster, rat and mouse origin, whereas the converse was true for those of cat and human origin. The interference and neutralization patterns suggested that the NBX virus was an env gene recombinant between A-X-MuLV and M-MuLV. The fact that NBX virus cross-reacted in radioimmunoassays with gp70s of both M-MuLV and Balb:virus-2 provides evidence for the recombinant nature of the NBX gp70-coding gene which was probably derived from both M-MuLV and a virus similar to Balb:virus-2 or A-X-MuLV. The presence of a unique antigenic determinant on the gp70 of NBX virus is also suggested. Both A-X-MuLV and NBX virus cross-reacted with type-specific p12s of M-MuLV and Balb;virus-2, suggesting that the gag gene coding for p12 of NBX virus was derived from the A-X-MuLV, which was itself a recombinant, its p12-coding gene being derived from both Balb:virus-2-like virus and M-MuLV. The NBX virus was not oncogenic when tested in newborn Balb/c mice. (Author abstract) (40 Refs)

51. DNA SEQUENCE RELATIONSHIP OF THE BABOON ENDOGENOUS VIRUS GENOME TO THE GENOMES O F OTHER TYPE C AND TYPE D RETROVIRUSES.

Cohen M, Rice N, Stephens R, O'Connell C
Biological Carcinogenesis Program, Frederick Cancer Res. Facility, Frederick, MD, 21701
J Virol; 41(3):801-812 1982

Baboon endogenous virus (BaEV) is a Type C retrovirus present in multiple proviral copies in the DNA of baboons. Although interspecies antigenic determinants present on reverse transcriptase and gag proteins are shared among all mammalian Type C viruses, no nucleic acid homology between BaEV and other Type C viruses (except RD-114) has been found in conventional liquid hybridization experiments. In this study, we used restriction fragments of cloned BaEV DNA immobilized on nitrocellulose to test for relatedness with [32P]cDNA's of various Type C and Type D viruses. We detected the following distant relationships previously found only through immunological and protein sequencing techniques: (i) eight Type C viral cDNA's and two Type D virus cDNA's were able to hybridize with cloned BaEV DNA; (ii) the eight Type C probes hybridized to restriction fragments spanning most of the BaEV genome, but only RD-114 hybridized to fragments within the 1.9 kilobases at the 3' end of the genome; (iii) the two Type D probes hybridized primarily to fragments within the 1.9 kilobases at the 3' terminus and weakly or not at all elsewhere; and (iv) [32P]cDNA's of several other oncornaviruses exhibited no homology with BaEV DNA. DNA sequence analysis has allowed us to orient the BaEV restriction map with the genetic map at both ends of the genome. Homologies between retroviral cDNA's and BaEV clone restriction fragments could thus be related to specific BaEV genes. These results are discussed relative to previously reported antigenic relatedness of retroviral proteins. The data suggest that BaEV represents an important link in oncornavirus evolution. (44 Refs)

52. EXPRESSION OF TRANSFORMING REGION OF MOLONEY MURINE SARCOMA VIRUS IN ESCHERICHIA COLI AS A FUSION PROTEIN WITH SMALL TUMOR ANTIGEN OF POLYOMA VIRUS.

Donoghue DJ, Hunter T
Tumor Virology Lab., The Salk Inst., P.O. Box 85800, San Diego, CA, 92138
Proc Natl Acad Sci USA; 79(3):800-804 1982

Bacterial expression of the transforming region of Moloney murine sarcoma virus, designated mos, was obtained as a fusion protein with a portion of the small tumor antigen of polyoma virus. This was accomplished by fusing the entire mos open reading frame, encoding a 41,000-dalton protein, with a plasmid that expresses a beta-galactosidase-polyoma fusion protein under lac operon control. The resulting plasmid directed synthesis of the predicted polyoma antigen-sarcoma virus fusion protein of 59,000 daltons. This protein was immunoprecipitated by an antipolyoma tumor antigen antiserum that recognized polyoma determinants at the NH2 terminus of the hybrid protein. This protein was also immunoprecipitated by an antiserum directed against a synthetic peptide containing the 12 COOH-terminal amino acids encoded by the mos open reading frame. This work confirms the existence of a long open reading frame in the mos gene and resolves a discrepancy between different nucleotide sequences for its COOH-terminal coding region. (Author abstract) (32 Refs)

53. MAMMARY TUMOR VIRUS (MTV) ANTIGEN EXPRESSION IN MALE GENITAL ORGANS FROM VARIOUS INBRED STRAINS OF MICE.

Imai S, Morimoto J, Tsubura Y
Second Dept. Pathology, Nara Medical Univ., Nara, Japan
Nara Igaku Zasshi; 32(5):570-573 1981

In an effort to demonstrate the route of extrachromosomal male transmission of MTV, MTV antigen expression in the epididymis and coagulating glands of the male genitalia of various strains of inbred mice was investigated with the aid of micro-immunodiffusion (micro-ID) test. The MTV expression was studied in the following strains of mice: high mammary cancer strains (GR, DD/Tbr, SHN, SLN, C3H/HeA), intermediate mammary cancer strains (DDD and KF), and low mammary cancer strains with low and moderate incidence of leukosis (but including AKR/RU). In the mice with positive micro-ID tests, the frequency of MTV antigen expression was generally lower in the epididymis than in the coagulating gland. The frequency of MTV antigen expression also depended on the mouse strains; high mammary cancer strains showed more frequent antigen expression in the male genital organs than low mammary cancer strains showed. Overall, there was no marked difference with regard to the frequency of antigen expression among the high mammary cancer strains. These findings confirmed that the male genitalia play an important role in paternal transmission of MTV. (17 Refs)

54. CELL SURFACE MODULATION IN MAMMARY CANCER.

Thompson K
Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, Oakland, CA, 94609
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Studies of the cell surface modulation which accompanies malignant transformation in mammary cancer are reviewed. Evidence for cell surface antigens (CSAs) of mouse and rat mammary tumors has not shown whether neoplastic transformation is associated with distinct tumor-specific antigens. Virus-induced mouse mammary tumors contain virus-specific antibodies, which are also present in normal mammary cells and nonmammary tissues. In rats with carcinogen-induced mammary tumors, the tumor loses an organ-specific antigen at the time of spontaneous dissemination. The experimental mammary tumors may also show gene derepression, which leads to the expression of abnormal differentiation antigens and/or fetal-type antigens. The tumors can acquire new CSAs not found in the tissue of origin and can acquire or lose CSAs already present in normal cells. Neoplastic transformation is a complex process, especially with regard to the cells which become neoplastic and the influence of host factors (genetic, hormonal, or immunologic). Interaction of these factors determines the malignant state. (283 Refs)

55. ISOLATION OF AN ANTIGEN FOR DIAGNOSIS OF ENZOOTIC CATTLE LEUKEMIA USING AGAR GEL IMMUNODIFFUSION TECHNIC.

Mateva V
Central Res. Veterinary Inst., Sofia, Bulgaria
Vet Med Nauki; 18(4):45-46 1981

A method of isolation of cattle leukemia virus antigen is described. The virus was isolated from the culture medium or from the cells of fetal lamb kidney infected with cattle leuke-

mia virus. The antigen formed a precipitation band with the leukemic sera. Activity and specificity of precipitation band did not differ from that produced by glucoprotein antigens. The antigen was effectively used for the diagnosis of enzootic cattle leukemia. (no Refs) (In BUL)

56. DIAGNOSIS OF BOVINE LEUKOSIS VIRUS INFECTION BY SOLID PHASE RADIOIMMUNOASSAY FOR VIRUS ANTIBODY.

Zajac V, Altaner C

Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia

Neoplasma; 28(6):661-668 1981

Solid phase radioimmunoassay for detection of anti-BLV antibodies in sera of infected animals is described. Viral antigens bound to the surface of polystyrene are able to selectively adsorb the antibodies from serum. Detection of bound antibodies quantitatively was done by 125I-labeled protein A from Staphylococcus aureus. Technical details of the assay are reported. The assay could be used as a competitive one as well. Two different methods for detection of anti-BLV antibodies were compared with solid phase RIA. The solid phase RIA is highly sensitive, specific and available for large-scale examination. The assay is recommended for early diagnosis of bovine leukosis. (Author abstract) (18 Refs)

57. ADSORPTION OF ROUS SARCOMA VIRUS TO GENETICALLY SUSCEPTIBLE AND RESISTANT CHICKEN CELLS STUDIED BY LASER FLOW CYTOMETRY.

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Dept. Microbiology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642

J Virol; 41(3):958-964 1982

Quantitative binding of Rous sarcoma virus (RSV) of different antigenic subgroups of chicken cells was examined by using a laser flow cytometer/cell sorter. RSV of subgroups A, C, and E, labeled with the fluorescent membrane probe rhodamine-18, bound 2 to 10 times more to genetically susceptible chicken embryo fibroblasts than to resistant cells, as measured by flow cytometry on a single-cell basis. This suggested that susceptible cells possess both specific and nonspecific receptors for virus adsorption, whereas resistant cells bind virus only by means of nonspecific sites. Polybrene at low concentration increased eightfold the binding of virus. Higher levels of Polybrene inhibited adsorption. Cell binding sites were saturable, and attachment of labeled virus could be partially blocked by preexposure of cells to unlabeled RSV. Virus surface glycoproteins played an important role in adsorption, since their removal with bromelain decreased binding of virus to susceptible cells. Maximal binding of RSV to both susceptible and resistant cells occurred within 10 min, although the level of binding was up to 10-fold higher for susceptible cells. Binding to all cell types showed a broad distribution. This implies that there are considerable differences in the number of virions bound per cell. (Author abstract) (29 Refs)

58. IMMUNOCHEMISTRY OF THE MOLONEY MULV GP71 MOLECULE - I. DISTRIBUTION OF ANTIGENIC DETERMINANTS ON THE PRODUCTS OF DIGESTION BY STAPHYLOCOCCUS AUREUS PROTEASE.

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Mol Immunol; 19(1):65-73 1982

The antigenic characterization of Moloney murine leukemia virus gp71 was carried out by cleavage with Staphylococcus aureus protease. The whole molecule and two fragments of 43,000 and 32,000 daltons were immunoprecipitated with monospecific anti-type, group and interspecies antiserum. The three native molecules were recognized by anti-type antibodies, but only the gp71 and the 32,000-dalton molecule seemed to retain group-specific antigenic determinants. No interspecies determinants were detected on the two products of digestion. A similar pattern of precipitation was found with SDS-denatured antigens. The results suggest that sequential structures contribute to the type-specific antigenic determinants, because they were not destroyed by SDS unfolding or by the change in the protein conformation that follows enzymatic cleavage. Interspecies determinants seem to be mainly conformational, since they disappeared from the whole molecule and the two peptides after the same treatment. Group-specific determinants appear to be intermediate; they disappeared after the conformational change on the native 43K but not on the 32K peptide and the monospecific anti-group antibody showed an intermediate ability to precipitate the SDS-unfolded antigens. (Author abstract) (36 Refs)

59. CONTRIBUTION TO EPIDEMIOLOGIC STUDIES OF BOVINE ENZOOTIC LEUKOSIS.

de Alencar RA, Rodrigues FM, Vianna WO

Instituto Biologico, Sao Paulo, Brazil

Biologico; 47(9):249-253 1981

An epidemiologic study of bovine enzootic leukosis (BLV) was performed, using cohabitation (CO), feeding (FE), or blood transfusion (BT). The BT experiment consisted of transferring 200 ml of blood from two serologically positive animals into two that were serologically negative. Immunodiffusion tests (IDT), performed on days 30, 60, 90, 120, and 180, using antigen Leukassay-B, all gave negative results. Eleven cows that were clinically negative for bovine leukemia virus (BLV) showed positive results with the IDT for blood, three showed positive results for colostrum 24 hr after delivery, and five for colostrum 48 hr after delivery. Blood of three of their heifers gave positive results 24 hr after birth and five gave positive results 48 hr after birth; 6 mo later none of the heifers gave positive results. The CO and FE of serologically positive or negative heifers for BLV and of cows that were serologically positive but clinically negative, did not endanger the heifers. Cross reaction was not observed between serum containing antibodies for BLV and serum containing antibodies for bovine diarrhea virus. (5 Refs) (In POR)

60. MCF-SPECIFIC MURINE MONOCLONAL ANTIBODIES MADE AGAINST AKR-247 MCF VIRUS RECOGNIZE A UNIQUE DETERMINANT ASSOCIATED WITH THE GP70-P15(E) COMPLEX.

Cloyd MW, Chesebro B, Portis JL, Weir M
Natl. Inst. Allergy and Infectious Diseases, Lab. Persistent Viral Disease, Rocky Mountain Lab., Hamilton, MT, 59840
J Virol; 41(3):1112-1117 1982

Hybridomas obtained from (NFS x AKR)F1 mice immunized with syngeneic cells infected with AKR-247 MCF virus produced antibodies specific for only AKR-247 or closely related MCF viruses which share a previously defined MCF antigen (MCFA-3). These monoclonal antibodies recognized a new type of viral antigenic determinant which appeared to be a conformational determinant associated with the env precursor polyprotein (pr80env) or its disulfide-linked gp70-p15(E) complex (gp80) but not with free gp70 or p15(E) or any other virion or virus-induced protein. (Author abstract) (26 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

61. A CRUCIAL ROLE OF THE H-2 D LOCUS IN THE REGULATION OF BOTH THE D- AND THE K-ASSOCIATED CYTOTOXIC T LYMPHOCYTE RESPONSE AGAINST MOLONEY LEUKEMIA VIRUS, DEMONSTRATED WITH TWO DB MUTANTS.

Stukart MJ, Vos A, Boes J, Meivold RW, Bailey DW, Melief CJ
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J Immunol; 128(3):1360-1364 1982

Previous studies have shown that the CTL response of C57BL/6(B6,H-2b) mice against Moloney leukemia virus is H-2 Db-restricted. In the current paper, we analyze the role of the H-2 Db locus in the CTL response against Moloney virus with two strains of mice carrying a mutation in the H-2 Db locus: B6.C-H-2bm13(bm13) and B6.C-H-2bm14(bm14). The influence of the D locus was seen at two levels. First, neither of the two Db-mutant targets could be recognized by Db-restricted CTL, as demonstrated with B10.A(4R) (Kk Db) and B6 (Kb Db) effector cells. Second, mutation at the Db locus strongly altered the character of the response, either by causing nonresponsiveness (bm 14 effector) or by increasing the Kb-associated co mponent of the CTL response (bm13 effector). These findings indicate that a single genetic element, H-2 D in this instance, determines the restriction specificity and regulates the magnitude of the CTL response. Cold target inhibition studies showed that either the restriction specificities of Dbm13 and Kb in the CTL response to this virus are indistinguishable or that the Dbm12-associated component of bm13 CTL is negligible. Experiments with (B6 x bm13)F1 and (B6 x bm14)F1 hybrid responding cells demonstrated a decisive role of H-2 on the antigen-presenting cells used for restimulation in vitro: primed F1 responding cells mounted CTL responses with the H-2 preference and magnitude of the parental cell type used for restimulation in vitro. Our findings strongly support the notion that Type I MHC molecules regulate the magnitude and specificity of the CTL response against viruses. (Author abstract) (29 Refs)

62. PRODUCT OF ADENOVIRUS TYPE 2 EARLY GENE BLOCK E1 IN TRANSFORMED CELLS ELICITS CYTOLYTIC RESPONSE IN SYNGENEIC RATS.

Raska K, Dougherty J, Gallimore PH
Dept. Pathology, Coll. Medicine and Dentistry New Jersey, Rutgers Medical Sch., Piscataway, NJ, 08854
Virology; 117(2):530-535 1982

The cytotoxic immune response to three well-characterized adenovirus Type 2 (Ad2)-transformed cell lines (A2T8, 50A, and T2C4) was studied in syngeneic LIS rats. Antibodies against the three virus-transformed lines were raised by hyperimmunization. Cytolytic T cells were generated by in vivo immunization and in vitro education with A2T8 and 50A cells. The complement-dependent antibody-mediated cytotoxicity with hyperimmune sera, T-cell cytotoxicity, and antibody-blocking effects in T-cell cytotoxicity assays indicate that these three Ad2-transformed cell lines share specific antigen. This observation was further confirmed by indirect immunofluorescence staining of the cell surface. Because it is absent in syngeneic LIS embryo fibroblasts and in syngeneic LIS cells transformed with EcoRI-C fragment of Ad12 DNA, this antigen appears to be Ad2 specific. Since the only Ad2 function shared and expressed by all three of these cell lines is the early gene block E1, it is concluded that its product or products elicit both humoral and T-cell cytolytic responses. (Author abstract) (17 Refs)

63. STIMULATION OF HUMAN LYMPHOCYTES WITH IRRADIATED CELLS OF THE AUTOLOGOUS EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINE. I. VIRUS-SPECIFIC AND NONSPECIFIC COMPONENTS OF THE CYTOTOXIC RESPONSE.

Wallace LE, Rickinson AB, Rowe M, Moss DJ, Allen DJ, Epstein MA
Dept. Pathology, Medical Sch., Univ. Bristol, Bristol BS8 1TD, England
Cell Immunol; 67(1):129-140 1982

Peripheral blood lymphocytes were cocultivated with irradiated cells of the autologous EB virus-transformed cell line at different responder:stimulator (R:S) ratios and the cytotoxic respo nse was assayed up to 12 days later. In cocultures set up at a R:S ratio of 4:1, the response from both EB virus antibody-positive (seropositive) and negative donors was dominated by a broad-ranging NK-like cytotoxicity which did not segregate within the E-rosette-forming subpopulation of effector cells. In contrast, cocultures set up at a R:S ratio of 40:1 and harvested after 10 to 12 days gave rise, in the case of seropositive donors only, to effector T-cell preparations which appeared to be both EB virus specific and HLA-A and B antigen restricted. Strong lysis of the autologous virus-transformed cell line and demonstrable activity against certain allogeneic HLA-A and/or B antigen-related virus-transformed lines occurred in the absence of any significant killing either of the corresponding lines from HLA-unrelated donors or of a variety of EB virus genome-negative target cells (K562, HSB2, KJAB) particularly sensitive to NK-like cytotoxicity; furthermore, lysis of the autologous cell line by these effector T cells was specifically inhibited by monoclonal antibodies binding to HLA-A, B and C antigens on the target cell surface. This work demonstrates that an HLA-restricted EB virus-specific cytotoxic T-cell response can indeed be induced in vitro by stimulation of fresh lymphocytes with autologous EB virus-transformed cells providing cocultures are set up at the correct R:S ratio. (Author abstract) (40 Refs)

64. HETEROGENEITY OF ALLOGENEIC RESTRICTION OF HUMAN CYTOTOXIC T CELL CLONES SPECIFIC FOR EPSTEIN BARR VIRUS.

Tanaka Y, Sugamura K, Hinuma Y
Inst. Virus Res., Kyoto Univ., Sakyo-ku, 606, Japan
J Immunol; 128(3):1241-1245 1982

Clones of human cytotoxic T cells (Tc) specific for Epstein Barr virus (EBV) were isolated from peripheral blood lymphocyte (PBL) cultures stimulated repeatedly with autologous EBV-transformed lymphoblastoid cell line (LCL) cells in vitro. The method employed to clone EBV-specific Tc was a limiting dilution technique utilizing T cell growth factor (TCGF). The EBV specificity of Tc clones was determined by showing that they were significantly cytotoxic for autologous LCL cells but not for either autologous PBL or (natural killer-sensitive) K-562 cells. Eight EBV-specific Tc clones derived from a single donor exhibited distinct cytotoxic patterns against allogeneic LCL targets. Two clones were cytotoxic to LCL targets sharing both HLA-A26 and B15 antigens with effectors, and killing by two other clones was strongly restricted to autologous LCL cells. The four remaining clones showed cytotoxicities against various allogeneic LCL targets irrespective of HLA antigen expression. Eight EBV-specific Tc clones derived from a second donor also exhibited a wide spectrum of cytotoxicity to allogeneic LCL targets. We conclude that EBV-specific Tc, induced in vitro, consist of a number of clones with respect to restrictions imp osed by the major histocompatibility complex. The determinants regulating these restrictions may include not only private HLA antigenic determinants that are defined by the HLA serotyping, but also undefined HLA antigenic determinants. (Author abstract) (30 Refs)

65. SHORT COMMUNICATIONS. THE INCREASED NATURAL KILLER SENSITIVITY OF EPSTEIN-BARR VIRUS (EBV)-SUPERINFECTED RAJI CELLS IS NOT DUE TO THE RECOGNITION OF SEROLOGICALLY DETERMINED EBV ANTIGENS BY THE EFFECTORS.

Patarroyo M, Klein E, Klein G
Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm, Sweden
Cell Immunol; 67(1):152-159 1982

The NK sensitivity of Raji cells was elevated after superinfection with the P3HR-1 strain of Epstein-Barr virus (EBV). The superinfected cells reacted with EBV antibody-positive sera and this was detectable by ADCC. F(ab')2 fragments from the antibody-positive sera blocked the ADCC reaction but did not affect attachment of lymphocytes and natural killing. This indicates that the EBV-determined membrane antigens that serve as targets for the reactivity with the sera are not responsible for the increased NK sensitivity. (Author abstract) (19 Refs)

66. STIMULATION OF HUMAN LYMPHOCYTES WITH IRRADIATED CELLS OF THE AUTOLOGOUS EPSTEIN-BARR VIRUS-TRANSFORMED CELL LINE. II. CYTOTOXIC RESPONSE TO REPEATED STIMULATION.

Allen DJ, Rickinson AB, Wallace LE, Rowe M, Moss DJ, Epstein MA
Dept. Pathology, Medical Sch., Univ. Bristol, Bristol BS8 1TD, England
Cell Immunol; 67(1):141-151 1982

Unfractionated peripheral blood mononuclear (UM) cells from adult donors of known serological status with respect to Epstein-Barr (EB) virus were exposed to four or more successive in vitro stimulations with irradiated cells of the autologous EB virus-transformed cell line at a responder:stimulator ratio of 4:1, and effector UM and T cells were prepared after each stimulation. Ten out of 14 seropositive donors and all four seronegative donors thus tested showed at best moderate cell proliferation over two or three stimulations only and a cytotoxic response which became dominated by non-E-rosette-forming cells active against the K562 cell line but not against EB virus-transformed lymphoblastoid lines. Cocultures from three other seropositive donors gave stronger proliferative responses and yielded effector cells dominated by a polyclonal E-rosette-forming population cytotoxic to the autologous and to certain allogeneic (both HLA-related and -unrelated) EB virus-transformed cell lines as well as to some but not all EB virus genome-negative hemopoietic cell lines of the kind sensitive to natural killer cells. With one other seropositive donor, this same repeated stimulation induced a quite different type of cytotoxic response, selectively amplifying an effector T-cell population which appeared on the basis of target cell specificit y and of sensitivity to monoclonal antibody blocking to be both EB virus-specific and HLA-A and B antigen restricted in its function. (Author abstract) (32 Refs)

67. INDUCTION AND INHIBITION OF THE IMMUNE RESPONSE TO TUMORS INDUCED BY SIMIAN VIRUS 40 (SV40).

Blasecki JW
Pharmaceuticals Div., Stine Lab., E.I. du Pont de Nemours and Co., Newark, DE, 19711
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

The growth or rejection of SV40-induced tumors in immunocompetent hosts is determined by a dynamic balance among cellular and humoral responses to the tumor and the effects of products shed from the tumor cells (apparently surface-associated antigens) on this balance. The first step in the immune response to the tumor seems to be the processing of SV40 tumor-specific transplantation antigens (TSTA) by the macrophages (or perhaps natural killer cells) and the presentation of TSTA to the T-lymphocytes. This leads to the appearance of sensitized T-cells having specific cytolytic activity against SV40 tumor cells. Cytotoxic antibodies apparently do not play a significant role in tumor rejection. The induction of immunity to SV40 TSTA is not the only aspect of the host-tumor interaction, but inhibition of the antitumor immune response is apparently critical to favoring tumor growth. SV40 TSTA seems to play an important role in abrogating specific cellular immunity to SV40 tumors in vivo. Antibody or antigen-antibody complexes seem to block cellular immunity to SV40 tumors at the cellular level. Progressive tumor growth apparently causes a specific or nonspecific suppression of helper T-cell activity. The suppression of antibody synthesis in tumor-bearing hosts may be involved in preventing antibody-mediated sequestration of tumor-associated antigens, thus enhancing tumor growth. Soluble blocking factors and suppressor cells also seem to be involved in regulating host immune responses to SV40-induced tumors. (217 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

68. AMYL NITRITE MAY ALTER T LYMPHOCYTES IN HOMOSEXUAL MEN.

Goedert JJ, Wallen WC, Mann DL, Strong DM, Neuland CY, Greene MH, Murray C, Fraumeni JF, Blattner WA

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Lancet; 1(8269):412-416 1982

To evaluate the recent outbreak of Kaposi's sarcoma (KS) and opportunistic infections in homosexual men, clinical, virological, and immunological data on 2 homosexual men with KS and on 15 healthy homosexual volunteers were collected. Both KS patients had regularly used amyl nitrite or butyl nitrite (AN); they had low helper/suppressor (H/S) T lymphocyte ratios before chemotherapy and high titers of antibody against cytomegalovirus (CMV). Eight of the 15 volunteers were regular AN users; 7 of the 8 had low H/S ratios due to larger than normal numbers of OKT8-positive suppressor cells and smaller numbers of OKT4-positive helper cells. In all eight AN users the fluorescence profile obtained with monoclonal antibody 9.6 (which detects the sheep E-rosette receptor) was bimodal, indicating a subpopulation of T cells with increased receptor density. A similar pattern was observed when OKT8, the antibody which detects cytotoxic suppressor cells, was used. Two of the seven men who did not use AN had abnormal fluorescence with reagent 9.6, and one of these also had a low H/S ratio. CMV-antibody titers were persistently high in 14 of the 15 healthy men, but the titers were not related to An use or T-cell abnormalities. The data suggest that nitrites may be immunosuppressive in the setting of repeated viral antigenic stimulation and may contribute to the high frequency of KS and opportunistic infections in homosexual men. (Author abstract) (35 Refs)

69. EFFECTS OF N-BUTYRATE ON EPSTEIN-BARR VIRUS-CARRYING LYMPHOMA LINES.

Anisimova E, Saemundsen AK, Roubal J, Vonka V, Klein G

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J Gen Virol; 58(part1):163-171 1982

The compound n-butyrate has been shown to induce Epstein-Barr virus (EBV) antigen synthesis in certain EBV-carrying lymphoma lines. We have studied the effect of n-butyrate on two EBV-positive Burkitt lymphoma lines by immunofluorescence and electron microscopy. In the producer line P3HR-1, the drug induced not only early antigen (EA) and virus capsid antigen (VCA) synthesis, as shown before, but also increased the number of cells containing virus particles. The transition from VCA expression to the formation of virus particles was much more effective in treated cells than in EBV antigen-producing cells of the same line. The productive cycle was associated with the development of characteristic morphological changes. In the non-producer Raji cells, n-butyrate induced EA in only a minor fraction of the cells. There were, however, clear signs of differentiation in the direction of plasma cells. Two days after the addition of n-butyrate 80% of the Raji cells could be classified as plasmablasts. After 72 hr, 20% of the cells appeared as typical plasma cells. (Author abstract) (33 Refs)

70. EFFECT OF THE ARGININE ANALOG CANAVANINE ON THE SYNTHESIS OF EPSTEIN-BARR VIRUS-INDUCED PROTEINS IN SUPERINFECTED RAJI CELLS.

Bayliss GJ, Wolf H

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J Virol; 41(3):1109-1111 1982

The addition of canavanine to cultures of superinfected Raji cells in the absence of arginine prevented the appearance of early antigens as defined by immunofluorescent staining. Addition of various amounts of arginine permitted the identification of at least three groups of proteins, each responding differently to the various concentrations of arginine-canavanine. (Author abstract) (9 Refs)

71. CYCLOSPORIN A ABROGATES PROLIFERATION OF T CELLS AND GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTION INDUCED BY EPSTEIN-BARR VIRUS.

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Dept. Immunobiology, Wallenberg Lab., Karolinska Institutet, Lilla Frescati, S-104 05 Stockholm, Sweden

Immunobiology; 160(3/4):321-329 1981

Cyclosporin A (CYA) promotes the outgrowth in vitro of Epstein-Barr-virus (EBV)-infected cells of immune donors. In the present study, the effects of CYA on the T-cell responses developed in an in-vitro EBV infection were studied. Cyclosporin A, by acting on the responder cells and not on stimulator cells, strongly inhibited the proliferation of T cells normally induced by EBV-infected autologous cells. Moreover, T cells from cultures not exposed to CYA exerted suppression on both alloantigen-induced DNA synthesis and PWM-stimulated immunoglobulin production of autologous peripheral blood mononuclear cells. In contrast, T cells from cultures treated with CYA exhibited significantly less or no suppressor activity as determined in both indicator systems. Finally, CYA abrogated the generation of cytotoxic T cells against EBV-infected autologous cells, whereas non-CYA-treated T cells killed the virus-transformed target cells. Both suppressor and cytotoxic T-cell functions are known to play an essential role in the control of EBV infection by limiting the continuous growth of the virus-infected cells. These results, therefore, strongly suggest that Cyclosporin A promotes the outgrowth of EBV-infected cells by abrogating the T-cell responses to the Epstein-Barr virus. (Author abstract) (23 Refs)

72. DEFINITION OF ALIEN H-2 DETERMINANTS ON A FRIEND LEUKEMIA BY ANALYSIS OF ALLOREACTIVITY OF CTL FROM PRIMARY MLC.

Greenberg PD, Cheever MA, Fefer A

Div. Oncology, RK-25, BB 1015 Health Sciences, Univ. Washington, Seattle, WA, 98195

J Immunogenet; 8(6):493-508 1981

An in vivo passaged subline (HFL/d) of Friend virus-induced leukemia of BALB/c origin expressed alien H-2 antigens as determined by reactivity with cytolytic T lymphocytes (CTL). This subline originated from an in vitro passaged subline HFL/d-tc, which when inoculated into BALB/c mice induced weak transplantation resistance. During adaptation to in vivo growth the new ascitic subline HFL/d apparently acquired the capacity to stimulate a cytotoxic response to H-2d antigens, but lost the ability to be lysed by CTL or antisera directed to its H-2d determinants. The presence of H-2d antigen of HFL/d recognizable by CTL was further confirmed by the

inhibition of lysis of H-2d targets by HFL/d cold targets. HFL/d stimulated in primary mixed lymphocyte culture (MLC) the generation of CTL which could lyse HFL/d through recognition of non-H-2d determinants not detectable on the parent in vivo passaged subline HFL/d-tc. The alloantigens on HFL/d were typed by generating CTL in primary MLC with HFL/d as stimulator, and measuring reactivity to targets with known H-2 antigens, and was confirmed by assessing recognition of HFL/d targets by CTL generated in primary MLC with stimulators expressing known H-2 antigens. HFL/d expresses Kd and Dd determinants derived from its strain of origin, alien determinants similar to Kb and Db antigens, and at least one additional determinant not present on normal H-2d or H-2b cells. CTL generated in MLC in a sensitive tool for examination of tumors for the presence of alien and/or cross-reactive H-2 determinants. (39 Refs)

73. CROSS-REACTIONS BETWEEN TUMOR CELLS AND ALLOGENEIC NORMAL TISSUES. INHIBITION OF A SYNGENEIC LYMPHOMA OUTGROWTH IN H-2 AND NON-H-2 ALLOIMMUNE BALB/C MICE.

Parmiani G, Sensi ML, Carbone G, Colombo M, Pierotti M, Balfinari D, Hilgers J, Hilkens J
Div. Experimental Oncology A, Istituto Nazionale Tumori, via G. Venezian 1, Milan, Italy
Int J Cancer; 29(3):323-332 1982

To test whether alloimmunization with H-2 and/or non-H-2 different normal tissues may increase the immunity to syngeneic tumors, groups of BALB/c (H-2d) mice were immunized with a series of allogeneic lymphoid cells and then challenged ip with syngeneic lymphoma cells. The outgrowth of otherwise lethal doses of the Moloney virus-induced lymphoma YC8 and of its clones was inhibited in BALB/c mice immune to DBA/2 (H-2d), C3Hf (H-2k), C3H.SW (H-2b), C3H.OH (H-2o2) and to B10 background tissue but not in mice immunized to A/He, BALB.K (H-2k) or BALB.B (H-2b) normal tissues. Anti-YC8 effect was also induced by immunizing BALB/c recipients with a pool of five different allogeneic cell lines which included C3Hf, C57BL/6J (H-2b), N:NIH (H-2q), B10.M (H-2f), and DBA/2 lymphoid cells. No growth inhibition of other BALB/c lymphomas induced by Moloney virus (LSTRA), x-rays (RL male I) or urethane (UR-I) was evident in alloimmune mice. In vivo transfer of growth inhibition of YC8 was obtained with BALB/c anti-B10.D2 peritoneal exudate cells in a Winn assay. The ability of these alloimmune lymphoid cells to delay significantly the survival time of BALB/c mice injected with the mixture of immune cell and YC8 cells was abrogated by anti-Thy 1.2 plus C' treatment. In addition, nu/nu BALB/c mice were unable to develop resistance to YC8 outgrowth after alloimmunization. The results of this study show that (1) syngeneic growth of a lymphoma can be prevented by autoimmunization with normal cells, (2) this cross-reaction involved non-H-2 antigens, (3) the phenomenon appeared to be mediated by T cells. (Author abstract) (35 Refs)

74. THE IN VITRO GENERATION OF H-2-RESTRICTED CYTOTOXIC T CELLS TO AKR/GROSS LEUKEMIA VIRUS-INDUCED TUMORS. I. REQUIREMENT FOR STIMULATION WITH ALLOGENEIC LEUKEMIA CELLS IN VIVO.

Green WR
Basic Immunology Program, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 128(3):1043-1049 1982

We have reported previously that vigorously lytic preparations of H-2-restricted C57BL/6 (H-2b) murine T cells specific for the subset of endogenous AKR leukemia virus-induced tumors that express the Gross cell surface antigen, including EmaleG2, can be raised. The generation of such CTL was accomplished by in vivo priming with an allogeneic AKR leukemic line followed by in vitro coculture of spleen cells from primed mice with irradiated GCSA tumors of H-2b haplotype. The results of the present report strongly suggest that the form of primary in vivo stimulation is crucial to the generation of such CTL. Examination of the four GCSA tumor cells of H-2b haplotype that are susceptible target cells in this system confirmed the requirement for in vivo alloantigenic stimulation. Thus, the two syngeneic tumor targets, EmaleG2 and EL4(S), were inefficient, whereas two H-2 congenic tumor targets, AKR H-2bSL1 and B.GV (BALB.B-derived), were efficient when used as priming cells. It appeared that the generation of H-2-restricted C57BL/6 CTL to AKR/Gross leukemia virus-induced tumors required concomitant in vivo stimulation with both target antigen and alloantigens. Although these alloantigens were not required to be H-2 encoded, it appeared they had to be present on the same cell that expressed the target antigens to exert their stimulatory effect. (33 Refs)

75. IMMUNE RESPONSES TO VARICELLA-ZOSTER IN THE AGED.

Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ (c/o Steele), Univ. Arkansas for Medical Sciences, 4301 W. Markham, Slot 512, Little Rock, AR, 72205
Arch Intern Med; 142(2):291-293 1982

Skin test reactivity and in vitro lymphocyte stimulation responses to varicella-zoster (VZ) were examined in a large normal population ranging in age from 6 mo to 93 yr. Waning of cellular immunity, as examined by skin delayed hypersensitivity, began at age 40 yr. Skin test responses to phytohemagglutinin, however, remained positive into the 8th decade of life. In vitro lymphocyte stimulation responses to VZ were usually positive (stimulation index greater than or equal to 2.5) until age 60 yr, after which time levels, as observed with nonimmune individuals, were often demonstrated. Antibody levels, as measured by fluorescent antibody to membrane antigen, remained positive into the 9th and 10th decades of life. This was especially so with a history of reactivation (zoster) VZ infections, while skin test and in vitro responses were rarely positive in those individuals. Thus cellular, as contrasted with humoral, immunity decrea ses with advancing age, which may account for a propensity to reactivation of VZ virus. (Author abstract) (18 Refs)

76. MECHANISM OF INTERFERON ACTION. DIFFERENTIAL EFFECT OF INTERFERON ON THE SYNTHESIS OF SIMIAN VIRUS 40 AND REOVIRUS POLYPEPTIDES IN MONKEY KIDNEY CELLS.

Daher KA, Samuel CE
(c/o Samuel) Section Biochemistry and Molecular Biology, Univ. California, Santa Barbara, CA, 93106
Virology; 117(2):379-390 1982

The effect of interferon (IFN) treatment on the synthesis of viral proteins was examined in BSC-1 monkey kidney cells singly and doubly infected with simian virus 40 (SV40) and reovirus. The pattern and amount of SV40 T antigen and reovirus lambda, mu, and sigma polypeptide synthesis was comparable in singly and doubly infected cells in the absence of IFN treatment. As determined by Yakobson et al and Kingman and Samuel SV40-specific RNA synthesis is inhibited by treatment of cells with IFN before infection, but is not inhibited by IFN

treatment after infection. IFN treatment initiated before infection inhibited the synthesis of both SV40 T antigen and reovirus polypeptides. However, SV40 T antigen synthesis was not inhibited in SV40 wt or tsA mutant-infected cells when treated with monkey kidney or human leukocyte IFN after infection. By contrast, reovirus polypeptide synthesis was markedly inhibited in BSC-1 cells treated with IFN after SV40 infection and superinfected with reovirus. SV40 infection did not rescue reovirus polypeptide synthesis from the inhibitory action of IFN, and reovirus infection did not alter the resistance of SV40 T antigen synthesis to IFN in cells IFN-treated after SV40 infection. Total cellular protein synthesis was not significantly affected by IFN treatment. These results suggest that the interferon-induced inhibitor(s) of protein synthesis discriminate between SV40 and reovirus mRNAs; the translation of SV40 mRNA, like most cellular mRNAs, is not affected under conditions where the IFN-induced inhibitor(s) significantly affect the translation of reovirus mRNA. (Author abstract) (40 Refs)

77. EXPRESSION OF TWO LATE ADENOVIRUS GENES IS ALTERED BY INTRODUCING ANTIBODIES AGAINST RIBONUCLEOPROTEIN INTO LIVING HELA CELLS.

Lenk RP, Maizel JV, Crouch RJ
Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, 9000 Rockville Pike, Bethesda, MD, 20205
Eur J Biochem; 121(3):475-482 1982

These experiments describe the effect on adenovirus gene expression of transfusing liposome-encapsulated antibodies directed against a 10-S ribonucleoprotein complex into infected HeLa cells. Immunoprecipitation studies demonstrate that this particular serum contains antibodies directed against particles containing U1 RNA and five polypeptides in the mol wt range of 45,000-60,000. The procedure of fusing liposomes successfully treats nearly all the cells in culture, and the transfused material has access throughout the cell. The IgG fraction from this serum is introduced into adenovirus-infected cells shortly before the transition from the early to the late stage of the lytic cycle; 19 hr after fusion the accumulated effects of the antibodies on late virus expression are examined by pulse-labeling cells with radioactive methionine and observing the synthesized proteins. While most late viral genes are expressed normally in treated cells, fiber synthesis is reduced to a very low level and hexon synthesis is reduced twofold. That most viral genes are expressed normally demonstrates that many cell activities (transcription, transport, processing and translation) are minimally affected. The effects on these two genes can be distinguished by varying the concentration of antibody transfused: interference with hexon synthesis occurs at a lower dosage than fiber. A simple interpretation of these results is that the antibody has bound to its antigen and prevented the latter from participating in its role in message processing. (Author abstract) (32 Refs)

OTHER RELATED STUDIES

78. BIOSYNTHESIS AND PROCESSING OF A HUMAN T LYMPHOCYTE ANTIGEN.

Bergman Y, Levy R
Howard Hughes Medical Inst., Stanford Univ., Stanford, CA, 94305
J Immunol; 128(3):1334-1340 1982

The biosynthesis and processing of Leu-1, a human T lymphocyte antigen, has been studied with the use of a monoclonal antibody. This molecule exists on the cell surface as a 67,000 mw glycoprotein. Through a series of pulse-labeling studies, in conjunction with the use of the antibiotic tunicamycin and the enzyme Endo-H, the details of glycosylation, processing, and deposition at the cell membrane were examined. The protein backbone of the molecule is 58,000 mw. High-mannose sugars are added to asparagine residues during synthesis. Within 20 min, these high mannose sugars are converted to complex type carbohydrates, including fucose. The fully processed glycoprotein appears at the cell surface within 30 min after synthesis. This sequence of events is similar to that for other cell surface glycoproteins, including HLA and vesicular stomatitis virus glycoprotein. (Author abstract) (35 Refs)

79. A NEW MURINE LYMPHOCYTE ALLOANTIGEN, LY-21.2, MAPPING TO THE SEVENTH CHROMOSOME.

Kennard J, Meruelo D
Irvington House Inst., Dept. Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
Immunogenetics; 15(3):239-250 1982

Using a monoclonal antibody raised by fusing spleen cells from A/J mice, immunized with B10.A splenocytes and lymph-node cells, with a BALB/c myeloma, we have described a new surface alloantigen, Ly-21.2. Ly-21.2 is present in varying amounts in all lymphoid tissues, is not detectable in the brain, kidney, lung or erythrocytes, and is found in only trace amounts in the liver. Strain distribution studies showed that Ly-21.2 is present in all strains examined, including B10, except the A strain and segregation analysis of (A/J x B10)F2 mice showed that Ly-21.2 expression (1) is encoded by one gene and (2) is linked to albinism on chromosome 7. Studies performed on mice developing T-cell leukemia showed that, regardless of the etiologic agent, Ly-21.2 expression increases dramatically in mice with overt leukemia. In addition, preliminary studies suggest that expression of Ly-21.2 is linked to increased susceptibility of mice to Friend-virus-induced erythroleukemia. (Author abstract) (27 Refs)

80. SPECIFICITY AND ROLE OF ANTIBODIES TO TUMOR ASSOCIATED ANTIGENS: ONE VIEW FROM THE LABYRINTH.

Klein PA
Tumor Biology Unit, Dept. Pathology, Coll. Medicine, Univ. Florida, Gainesville, FL, 32610
The Handbook of Cancer Immunology: Volume 9- Humoral Immunity in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 289 pp., 1981.

Animals bearing some types of tumors develop antibodies in response to tumor-associated antigens (TAAs). The net results of the host-tumor-TAA interaction range from inhibition to promotion of local tumor growth and metastatic spread. The natures of these TAAs are poorly understood. Cell-mediated mechanisms depend on T-lymphocytes are important in host reactions to immunogenic transplantable tumors. Only highly immunogenic tumors induced by certain DNA viruses elicit immune surveillance reactions Because of the major differences between transplantable animal tumors and spontaneous human tumors, the applicability of these studies on tumor immunology to clinical research is not clear. (91 Refs)

81. DIFFERENTIAL LYSIS OF ENDOGENOUS AND ACTIVATED NATURAL KILLER CELLS BY ANTI-NK-1.2 ANTIBODY AND COMPLEMENT.

Kumar V, Barnes MC, Bennett M, Burton RC
Dept. Pathology, Boston Univ. Sch. Medicine, Boston, MA, 02118
J Immunol; 128(3):1482-1484 1982

Data indicating that natural killer (NK) cells activated by a variety of agents, including lymphocytic choriomeningitis virus, polyinosinic-polycytidilic acid, and interferon, showed markedly diminished expression of the cell surface NK cell-specific alloantigen NK-1.2, to the point where these cells may be totally resistant to lysis by anti-NK-1.2 serum and complement, are presented. (15 Refs)

82. PHORBOL ESTER-INDUCED DIFFERENTIATION OF A NON-T, NON-B LEUKEMIC CELL LINE: MODEL FOR HUMAN LYMPHOID PROGENITOR CELL DEVELOPMENT.

LeBien TW, Bollum FJ, Yasmineh WG, Kersey JH
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 609 Mayo, Minneapolis, MN, 55455
J Immunol; 128(3):1316-1320 1982

The phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was tested for its ability to induce phenotypic changes in the human non-T, non-B ALL cell line REH. Cells were cultured with nanogram concentrations of TPA for up to 48 hr, and were analyzed by indirect immunofluorescence with a panel of monoclonal antibodies and an antibody to the enzyme terminal deoxynucleotidyl transferase (TdT). TPA induced REH cells to express the leukemia-associated antigen, p24 (detected with monoclonal antibody BA-2; p24/BA-2) by 8 hr of culture, with induction complete by 24 hr. TPA-treated cells also underwent a concomitant decrease in the expression of TdT when analyzed enzymatically or by immunofluorescence. Analysis of TPA-treated cells with monoclonal antibodies BA-1 (detecting a B cell-associated antigen), 7.2 (detecting a monomorphic HLA-DR antigen), or OKT11 (detecting a structure closely associated with the E receptor) showed no change compared to controls. In addition there was no detectable cytoplasmic immunoglobulin in control or TPA-treated cells. These results show clearly that TPA is capable of inducing phenotypic changes in REH cells. Such changes may reflect the differentiation-linked expression of antigens present in normal bone marrow lymphoid progenitor cells. (Author abstract) (41 Refs)

83. PRODUCTION OF MONOCLONAL ANTIBODY ALPHAPRO3 RECOGNIZING A HUMAN PROSTATIC CARCINOMA ANTIGEN.

Ware JL, Paulson DF, Parks SF, Webb KS
Dept. Surgery, Div. Urology, Duke Univ. Medical Center, Durham, NC, 27710
Cancer Res; 42(4):1215-1222 1982

The monoclonal antibody alphaPro3 recognizes an antigen concentrated in human primary prostatic carcinoma tissue removed surgically. Although the antigen was detectable in extracts of human normal and malignant nonprostatic tissue, as well as in benign prostate tissue, quantitative absorption analysis revealed a substantially greater quantity of the antigen in malignant prostate tissue. The antigen recognized by alphaPro3 in primary prostatic carcinoma has an apparent nonreduced molecular weight of 175,000 and an apparent subunit molecular weight of 54,000. This antigen, p54, appears to be present on the surface of cultured prostatic tumor cells of the PC-3 cell line, but its location in vivo has been defined. Successful competition between alphaPro3 and prostatic carcinoma patient serum immunoglobulin for a Mr 54,000 antigen (reduced molecular weight) present in prostatic carcinoma tissue extract suggests that p54 may play a significant role in the immunobiology of prostatic carcinoma. AlphaPro3 has potential as a sensitive probe for an antigen relevant to human tumor biology. (Author abstract) (46 Refs)

84. THE HANDBOOK OF CANCER IMMUNOLOGY: VOLUME 8: TUMOR ANTIGENS: STRUCTURE AND FUNCTION.

Waters H
NIH, Bethesda, MD
The Handbook of Cancer Immunology: Volume 8: Tumor Antigens: Structure and Function. New York, Garland STPM Press, 418 pp., 1981.

Structural and functional aspects of tumor antigens are reviewed. Mechanisms of reactions between lymphocytes and antigens are discussed. Characteristics of Ia antigens in mice and humans are presented and the significance of these antigens is considered. Histocompatibility antigens and tumor-associated antigens in plasma and urine are discussed and their diagnostic significance evaluated. Molecular structure and mechanisms of antibody-antigen interactions are outlined. Other topics include the use of cell membranes to assess phenotypic expression, masking of cancer-cell surface antigens, cell surface modulation in mammary cancer, antigen activation of T cells, assay and structure of carcinoembryonic antigens, induction of immune response to tumors induced by simian virus 40, and tumor-associated immunosuppressive serum proteins. Concentration and distribution of antigens are related to normal and pathological conditions. Discussion includes review of literature, presentation of original findings, and speculation on future research efforts. Converging and diverging viewpoints are expressed. (1659 Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. ISOLATION AND CHARACTERIZATION OF RETROVIRUS FROM CELL LINES OF HUMAN ADULT T-CELL LEUKEMIA AND ITS IMPLICATION IN THE DISEASE.

Yoshida M, Miyoshi I, Hinuma Y
Dept. Viral Oncology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
Proc Natl Acad Sci USA; 79(6,part1):2031-2035 1982

A retrovirus (ATLV) was unequivocally demonstrated in human adult T-cell leukemia (ATL) cell lines by density (1.152-1.155 g/cm3) in a sucrose gradient, reverse transcriptase

HE 20. 3173/2:

activity insensitive to actinomycin D, RNA labeled with [3H]uridine, and specific proteins with mol wt of 11,000, 14,000, 17,000, 24,000, and 45,000. Furthermore, cDNA prepared by endogenous reaction with detergent-treated virions hybridized to 35S RNA containing poly(A), which was inducible by IdUrd treatment of a T-cell line derived from leukemic cells of the ATL, and the integrated form of ATLV proviral DNA was detected in T-cell lines derived from ATL. The ATLV proviral DNA was also detected in fresh peripheral lymphocytes from all five patients with ATL tested so far but not in those from healthy adults. On the other hand, ATLV protein of Mr 42,000 was found to be at least one of the ATL-associated antigen(s) that were previously detected in ATL leukemic cells by all sera from patients with ATL. These findings on the close association of ATLV protein and proviral DNA with ATL are direct evidence for the possible involvement of the retrovirus ATLV in leukemogenesis of human ATL. (Author abstract) (18 Refs)

2. CHILDREN'S BRAIN TUMOUR CELLS PRODUCE RNA PARTICLES WITH INCOMPLETE RETROVIRUS CHARACTERISTICS.

Thorne HJ, Jose DG, Adams FC, Coelen RJ, Whitehead RH, Klugg G
Clinical Immunology and Immunogenetics Unit, Cancer Inst., Melbourne, Victoria, Australia
Oncology; 39(3):156-162 1982

Short-term cultures of cells from human brain tumors have been reported to synthesize RNA particles of density in the range characteristic of C type RNA retroviruses, with associated DNA polymerase activity. Fresh tumor cells obtained from six children with astrocytoma and seven children with medulloblastoma together with one sample of normal brain tissue and normal leukocytes from brain tumor patients were assayed by several characteristics for the presence of primate retrovirus. One of six (17%) astrocytomas and four of seven (57%) medulloblastomas released RNA particles which banded in sucrose gradients at a density of 1.16-1.18 g/cm3 together with a short segment of DNA, which was eliminated by prior ribonuclease treatment and two proteins of 28k and 16k daltons. These findings were compatible with the presence of a primate retrovirus. Immune coprecipitation of 125I-labeled proteins from the 1.16-1.18 g/cm3 gradient region failed to show any reactivity with antisera to p28 core antigens or the p70 reverse transcriptase antigens of simian sarcoma virus, baboon endogenous virus or Mason Pfizer virus. Assays for DNA polymerase activity in culture supernatant fluid showed only a low amount of activity with template preference not characteristic of the retroviral reverse transcriptase enzyme. (Author abstract) (21 Refs)

3. ANTIBODY PATTERN TO HUMAN CYTOMEGALOVIRUS IN PATIENTS WITH ADENOCARCINOMA OF THE COLON.

Avni A, Haikin H, Feuchtwanger MM, Sacks M, Naggan L, Sarov B, Sarov I
(c/o I. Sarov) Virology Unit, Faculty Health Sciences, Ben Gurion Univ. Negev, Beer Sheva, Israel
Intervirology; 16(4):244-249 1981

The role of human cytomegalovirus (CMV) was examined according to serological patterns in 37 patients with adenocarcinoma of the colon (ACC). The sera were examined for the presence of IgG antibodies by the immunoperoxidase antibody to membrane antigen (IPAMA) method and by the complement-fixation (CF) test. Antibody determinations were also performed by the IPAMA method for three other members of the herpesvirus group: Epstein-Barr virus (EBV), herpes simplex virus (HSV) and varicella-zoster virus (VZV). Comparison groups included normal subjects, ACC patients treated with chemotherapy, and patients operated on for benign diseases. No significant difference was found in the geometric mean titers (GMTs) for CMV and the other herpesvirus in the sera of nontreated ACC patients when compared with the control groups. However, a significantly elevated antibody titer to CMV was found in chemotherapy-treated ACC patients by both the IPAMA and CF methods. In this group, elevated titers were found by the IPAMA method for EBV and HSV, but not for VZV. The significance of serological studies in elucidating the role of CMV in ACC patients is discussed. (Author abstract) (30 Refs)

4. VULVAR INTRAEPITHELIAL NEOPLASIA: THE CONCEPT AND ITS APPLICATION.

Crum CP
Div. Obstetrical and Gynecological Pathology, Columbia Univ. Coll. Physicians and Surgeons, 630 West 168th St., New York, NY, 10032
Hum Pathol; 13(3):187-189 1982

The role of herpes simplex virus type 2 and human papilloma virus (HPV) in vulvar intraepithelial neoplasia (VIN) are discussed. Diagnosis and classification of VIN based on immunoperoxidase localization of HPV antigens and Feulgen DNA microspectrophotometric technics are described. Use of the technic allows non-neoplastic or infectious processes to be distinguished from VIN. The clinical approach to VIN is discussed. Local removal of lesions by local excision, skinning vulvectomy, and laser with adequate follow-up are commonly used to treat VIN. 5-Fluorouracil treatment of VIN has met with limited success. (24 Refs)

5. HEPATITIS B INFECTION AND THE PREVENTION OF PRIMARY HEPATOCELLULAR CARCINOMA: STUDIES IN SENEGAL.

Froment A, Larouze B, Feret E, Marinier E, Moustapha Sow A, London WT, Blumberg BS
(c/o Blumberg) Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Prog Med Virol; 27:133-136 1981

Continuing studies of hepatitis B (HBV) infection in Senegal include mother to child infection antigenic studies, studies of whole villages and family units within them, family studies of patients with primary hepatocellular carcinoma and families with cirrhosis or chronic active hepatitis, and studies of the interaction of protein-calorie malnutrition in children with responses to HBV. Early administration of vaccine could drastically reduce the incidence of HBV, although its effect on malnourished children is unpredictable. (11 Refs)

6. HEPATIC HUMORAL AND MORPHOLOGIC STUDY IN NON-HODGKIN'S LYMPHOMA.

Garay GE, Zeilikoff R, Richard LA, Balletti N, Koch O, Domecq P, Brush E, Pavlovsky S
Departamento de Oncohematologia, Academia Nacional de Medicina, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):49-56 1981

Hepatic (HE) humoral and morphologic study was performed in 21 untreated patients (14 males, 7 women; 28-71 yr old) with non-Hodgkin's lymphoma; 12 had good and 9 had bad histologic prognosis according to Rapapport's classification. According to Ann Arbor clinical staging, 2 patients were Stage Ia, 3 were Stage IIa, 3 were Stage IIb, 8 were Stage

IIIa, 2 were Stage IIIb, 3 were Stage IVa, and 2 were Stage IVb. Tests performed included percutaneous HE biopsy, echography, bromosulfophthalein clearance, protein and prothrombin time, HE enzymes, surface antigen, surface antiantigen antibody (AA) and hepatitis B core AA and autoantibodies. HE biopsy failed in 4/17 patients, 5/17 were normal, 3/17 showed HE lymphomatous infiltrations (HLI), 7/17 fatty changes, 1/17 mild cholestasis, and 1/17 vacuolization and nuclear anisokaryosis. Echography indicated changes in patients with HLI. Prothrombin time and K1 were most indicative parameters for HLI and other non specific morphologic changes. Phosphohexose isomerase and lactic acid dehydrogenase were increased in lymphomatous disease, but not in HE disease; they decreased in patients, who were in complete remission (CR) after receiving polychemotherapy Patients, who did not achieve CR or died (almost half), showed significant number of changes in HE function in contrast to those in CR. (31 Refs) (In SPA)

7. FINAL CASE REPORTING FROM THE UGANDAN PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN EBV AND BURKITT'S LYMPHOMA.

Geser A, DeThe G, Lenoir C, Day NE, Williams EH
International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon, France
Int J Cancer; 29(4):397-400 1982

A prospective epidemiological study was carried out in the West Nile District of Uganda from 1972 to 1979 in order to investigate the etiological role of the Epstein-Barr virus (EBV) in Burkitt's lymphoma (BL). By 1976, 14 BL cases had been detected among the 42,000 children originally bled in the study area. Testing of sera from BL candidates and neighborhood controls showed that children who develop BL later have EBV/VCA titers several dilutions higher than their age- and sex-matched neighbors. This appearance of a strong EBV activity long before BL development was taken as evidence of a causal role of EBV in BL in order to add to the unique material of pre-bled BL cases, BL detection was continued up to March 1979 when field work became impossible in Uganda. Two additional pre-bled BL cases were found during this extension of the study. The serological and virological evaluation of these additional cases showed that the EBV/VCA titers, but not the EA and EBNA titers, were about two dilutions higher in the BL candidates than in the controls. Hybridization assays showed that both lymphomas contained EBV/DNA in the tumor cells. These additional results thus confirm the findings in the first 14 cases and strengthen the epidemiological evidence for a causal role of the EBV in endemic BL. (Author abstract) (10 Refs)

8. EPSTEIN-BARR VIRUS-INDUCED B-CELL LYMPHOMA AFTER RENAL TRANSPLANTATION: ACYCLOVIR THERAPY AND TRANSITION FROM POLYCLONAL TO MONOCLONAL B-CELL PROLIFERATION.

Hanto DW, Frizzera G, Gajl-Peczalska KJ, Sakamoto K, Purtilo DT, Balfour HH, Simmons RL, Najarian JS
Dept. Surgery, Univ. Minnesota, Box 171, Mayo Memorial Building, Minneapolis, MN, 55455
N Engl J Med; 306(15):913-918 1982

Epstein-Barr virus (EBV)-associated polyclonal bone marrow-derived B-cell lymphoproliferative disease is reported in a 12-yr-old by who had been a renal transplant recipient. The disease regressed twice during acyclovir treatment. The patient underwent three renal transplants, each resulting in rejection, for kidney failure secondary to Henoch-Schonlein purpura. Sixteen wk after a fourth transplantation, the patient was readmitted for a left preauricular mass and soaking night sweats. Biopsy of the mass demonstrated a polymorphic B-cell lymphoma with surface immunoglobulin and cytoplasmic immunoglobulin of polyclonal specificity. Over 80% of the large atypical cells were positive for Epstein-Barr nuclear antigen. Bone marrow involvement was confirmed. Azathioprine was discontinued and prednisone reduced to maintenance dose, but malaise, sore throat, anorexia, and cervical lymphadenopathy progressed. Fever spikes to 39 and 40 C continued. Acyclovir therapy (7 day, 500 mg/square meter body surface area every 8 hr, iv) effectively controlled the symptomatology. Discontinuance of acyclovir resulted in the return of symptomatology. While three courses of acyclovir provided temporary benefit, the patient died 43 wk after final transplantation. A histologic change of the lesion from polymorphic lymphoma to monomorphic immunoblastic proliferation had apparently occurred; for effective control acyclovir may need to be combined with other forms of therapy, such as interferon, cytoxic drugs, or radiation. (20 Refs)

9. ASSOCIATION OF THE EPSTEIN-BARR VIRUS WITH NASOPHARYNGEAL CARCINOMA.

Henle W, Henle G
Joseph Stokes, Jr., Res. Inst., Childrens Hosp. Philadelphia, Philadelphia, PA, 19104
Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Association found using an immunofluorescence test (IFT) for detection of Epstein-Barr virus (EBV) in Burkitt's lymphoma and for titration of antibodies to the virus is discussed. Antibodies measured in the original IFT were directed against viral capsid antigen, which is present in every virus-producing cell. Approaches used for linking a virus with a human malignancy have been detection of viral fingerprints in the tumor, malignant transformation of normal cells by the virus in vitro, induction of tumors in non-human primates or other animals by injection of the virus, and demonstration of a broad spectrum and higher titers of antibodies to virus-related antigens in patients compared to controls and their relation to prognosis of the patients. EBV-specific serology may serve to monitor the effectiveness of therapy and to warn of imminent relapses or metastases before they become clinically evident. (20 Refs)

10. REACTIVATION OF CHRONIC HEPATITIS B VIRUS INFECTION BY CANCER CHEMOTHERAPY.

Hoofnagle JH, Dusheiko GM, Schafer DF, Jones A, Micetich KC, Young RC, Costa J
Liver Diseases Section, NIH, Building 10, Room 4-D-52, Bethesda, MD, 20205
Ann Intern Med; 96(4):447-449 1982

Two patients referred for cancer chemotherapy were found to be chronic, asymptomatic hepatitis B surface antigen (HBsAg) carriers. They had normal serum aminotransferase levels, but their sera were positive for HBsAg and antibody to hepatitis B e antigen. Both patients developed acute, icteric hepatitis within 3 mo of starting cycled chemotherapy. In both cases, the disease seemed to be caused by a recurrence of Type B hepatitis; it was accompanied by a marked increase in HBsAg titer and the appearance of hepatitis B virus DNA and DNA polymerase in the serum. One patient had a second episode of acute hepatitis after a second course of chemotherapy,

but both patients ultimately recovered and became seronegative for HBsAg. Thus, it seems that cancer chemotherapeutic agents can reactivate Type B hepatitis in asymptomatic HBsAg carriers. This reactivation is most likely due to an increase in hepatitis B virus synthesis followed by a rebound in host immune responses to hepatitis B virus infection when therapy is stopped. Such a phenomenon could have important implications for the therapy of chronic hepatitis B virus infection. (Author abstract) (12 Refs)

11. HEPATOCELLULAR CARCINOMA IN RURAL SOUTHERN AFRICAN BLACKS.

Kew MC, Geddes E

Dept. Medicine, Univ. Witwatersrand Medical Sch., Hospital Hill, Johannesburg 2001, South Africa

Medicine (Baltimore); 61(2):98-108 1982

The clinical presentation and natural history of hepatocellular carcinoma, as well as its association with cirrhosis and the hepatitis-B virus surface antigen, were studied in 585 Black males living in rural areas of southern Africa. In addition, the value of serum alpha-fetoprotein concentrations, serum biochemical changes, and various radiologic, isotopic and sonographic techniques in the diagnosis of hepatocellular carcinoma in this population was reviewed. The mean age of the patients was 35 yr and 40% of them were less than 30 yr of age. The most common presenting complaints were upper abdominal pain, swelling of the abdomen, wt loss and weakness. Rupture of the tumor with acute intraperitoneal hemorrhage occurred in 10% of the patients. The liver was almost always enlarged and focal tenderness was usual. An arterial bruit was heard over the liver in 23% of the patients. Ascites and splenomegaly were each present in about one-half of the patients, and 28% were jaundiced. Progressive muscle wasting was almost invariable. The tumor was rarely resectable and the patients did not respond to radiation therapy or cancer chemotherapy: the mean survival from the onset of symptoms was 11.1 wk and from the time of diagnosis 6 wk. Macronodular cirrhosis was present in the non-tumorous liver tissue at necropsy in 60% of the patients. The hepatitis-B surface antigen was detected in the serum of 62% of the patients. It was more common in younger patients, but was not related to the presence of alpha-fetoprotein. HBs antigenemia was equally common in patients with and without cirrhosis. Alpha-fetoprotein was present in high concentration in the serum of 67% of the patients and provided an excellent indicator of the diagnosis of hepatocellular carcinoma. It was more commonly found in younger patients. Biochemical changes were non-specific and did not differentiate hepatocellular carcinoma from cirrhosis or other mass lesions in the liver. Chest radiographs showed elevation of the right hemidiaphragm in 30% of the patients and multiple pulmonary metastases in 25%. One or more defects were invariably seen on isotope liver scans but the picture was not diagnostic of hepatocellular carcinoma. Blood flow scintigraphy usually showed the lesions to be vascular. Echogenic or partly echogenic and partly anechoic lesions with ill-defined edges were demonstrated on ultrasonography. Computerized axial tomograms and hepatic arteriography were useful in assessing the extent of the tumor in relation to possible resection. (Author abstract) (28 Refs)

12. HEPATITIS B ANTIGEN IN SERUM OF THE PATIENTS WITH CHRONIC LIVER DISEASES AND MALIGNANT HEPATOMA.

Libman E, Stojsic S, Marton B, Lemberger J

Sluzba za internisticke bolesti, Interno odeljenje, Medicinski centar, Subotica, Subotica, Yugoslavia

Med Pregl; 34(9/10):389-392 1981

Serum radioimmunoassay (RIA) was used for the determination of hepatitis B surface antigen (HBsAg). Serum of 30 healthy controls (HC), of 50 blood donors (BD: 20-54 yr old), of 96 patients with chronic persistent hepatitis (CPH), of 8 with aggressive hepatitis (AH), of 95 with alcoholic hepatic cirrhosis (AHC), of 10 with postnecrotic hepatic cirrhosis (PHC), and of 20 with malignant hepatoma (MH) was analyzed for HBsAg. RIA was also used for the determination of alpha-fetoprotein (AFP). Increased values of HBsAg were observed in 6 of the BD, in 22 of the patients with CPH, in 5 with AH, in 4 with AHC, in 3 with PHC, and in 1 with MH. Increased values of AFP were found in 2 patients with AH, in 6 with AHC, in 6 with PHC, and in 14 with MH. Concentrations of AFP were 18-11,812 nanog/ml in patients with MH. One patient with primary MH and increased value of HBsAg, did not have increased value of AFP. (28 Refs) (In SCR)

13. PRIMARY LIVER CARCINOMA IN CHONGQING.

Liu W, Yuan A, Jin H, Hong D, Luo Y, Zhao S

Dept. Internal Medicine, Affiliated First Hosp., Chinese PLA Third Military Medical Coll., People's Republic of China

Zhonghua Neike Zazhi; 20(7):392-396 1981

Results of a mass-screening and follow-up study are described for primary liver cancer in Chongqing. A higher incidence of liver cancer was found to be associated with males 50 and 60 yr old, history of liver diseases such as hepatitis B, high levels of alpha-fetoprotein, and a positive test for hepatitis B surface antigens. Based on these findings, the importance of the follow-up of high-risk individuals and the early diagnosis of liver cancer is stressed. (3 Refs) (In CHI)

14. ASPECTS OF RESEARCH STUDIES ON LIVER CARCINOMA.

Zhen Y

Shanghai Inst. Cell Biology, Academia Sinica, Shanghai, People's Republic of China

Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Studies with human liver carcinoma (HLC) and rat hepatoma are summarized. In vitro cultured HLC cell lines, fetal antigens in HLC, localization of surface and core antigen of hepatitis B virus in human hepatoma, cell-mediated cytotoxicity and immune RNA studies in human hepatoma, and experimental hepatoma research are discussed. A transplantable rat hepatoma was established by feeding Wistar rats with diethylnitrosamine in drinking water. The hepatoma exhibited fetal characteristics, including alpha-fetoprotein production, fetal isozyme expression, and the presence of membrane-associated fetal antigen. Research using these model systems and liver material derived from animals during carcinogenesis and from regenerated and fetal livers is described. (19 Refs)

15. A VIRUS-RELATED PROTEIN IN HUMAN BREAST CANCER.

Spiegelman S, Mesa-Tejada R, Ohno T, Ramanarayanan M, Nayak R, Baush J, Fenoglio C, Keydar I

Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY

Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Examination of validity of the viral transformation mechanism is described. Topics discussed include testing the diagnostic utility of particle proteins with the murine mammary model, immunohistological localization of murine mammary tumor virus in mouse mammary tumors, immunological detection in human breast carcinomas (BC), malignant breast tissues, normal and benign breast tissues, apocrine metaplasia, malignancies other than BC, specificity of the immunoperoxidase reaction in human BC, and the role of sugar residues in the crossreactivity of 52,000 dalton glycoprotein with the human breast cancer antigen. Experiments showed that particles detected possess the key diagnostic features as well as the density and size of oncornaviruses. (37 Refs)

16. SERA FROM PATIENTS WITH UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA CONTAIN A FACTOR WHICH ABROGATES SPECIFIC EPSTEIN-BARR VIRUS ANTIGEN-INDUCED LYMPHOCYTE RESPONSE.

Sundar SK, Ablashi DV, Kamaraju LS, Levine PH, Faggioni A, Armstrong GR, Pearson GR, Krueger GR, Hewetson JF, Bertram G, Sesterhenn K, Menezes J

(c/o Menezes) Lab. Immunovirology, Pediatric Res. Center, St. Justine Hosp., 3175 Cote St. Catherine, Montreal (Quebec) H3T 1C5, Canada

Int J Cancer; 29(4):407-412 1982

A unique association of Epstein-Barr virus (EBV) with the undifferentiated nasopharyngeal carcinoma (NPC) is a well acknowledged phenomenon. We report here the detection of a factor present in the sera of NPC patients which inhibits the blastogenic response of lymphocytes from EBV seropositive individuals to EB virions or soluble antigens. This lymphocyte-stimulation inhibitor (LSI) was found to be associated with the IgA fraction of the serum immunoglobulins. No inhibitory activity was detected in the sera and their immunoglobulin fractions from healthy (both EBV-seropositive and seronegative) individuals and patients with other carcinomas of the head and neck region. Interestingly, the IgA-LSI was absent in the sera of NPC patients who were successfully treated and remained in remission, while it was readily detectable in the sera of NPC patients in relapse. LSI-positive IgA fractions did not inhibit mitogenic response of lymphocytes to phytohemagglutinin. Taken together, the data presented suggest that LSI is a specific inhibitor of the response of sensitized lymphocytes to EBV antigens and that it may indeed represent a marker of great clinical significance regarding undifferentiated nasopharyngeal carcinoma, particularly for its prognosis. (Author abstract) (36 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

17. INDUCTION OF SISTER CHROMATID EXCHANGE BY POLYOMA LARGE VIRAL TUMOR ANTIGEN IN TRANSFORMED RAT FIBROBLASTS.

Brown EH, Basilico C

Dept. Pathology, New York Univ. Sch. Medicine, New York, NY, 10016

Cancer Res; 42(5):1909-1912 1982

The frequency of sister chromatid exchange (SCE) was determined in rat fibroblasts transformed by wild-type polyoma virus or by a mutant temperature sensitive for viral large tumor antigen function (ts-a). Elevated SCE frequencies were observed in two wild-type transformed cell lines growing at 37 C and in four ts-a-transformed lines upon growth at the permissive temperature for large viral tumor antigen (33 C). The increase in SCE frequency in ts-a-transformed cells at 33 C was reversed by growth at 39 C (nonpermissive for T-antigen function). An increase in SCE at 33 C was not observed in untransformed cells or in a ts-a-transformed cell line which makes a defective large viral tumor antigen. These results suggest that large viral tumor antigen can induce SCEs. Since large viral tumor antigen is also responsible for amplification of integrated viral DNA sequences (4), we tried to correlate this phenomenon with the increased SCE frequency. However, increasing SCE artificially by growing cells in the presence of 12-O-tetradecanoylphorbol-13-acetate did not result in amplification of integrated viral DNA in the absence of large viral tumor antigen function. Thus, there is no simple causal relationship between increased SCE and amplification. (Author abstract) (18 Refs)

18. ESTABLISHMENT AND CHARACTERIZATION OF SV40-TRANSFORMED HUMAN BREAST EPITHELIAL CELL LINES.

Chang SE, Keen J, Lane EB, Taylor-Papadimitriou J

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

Cancer Res; 42(5):2040-2053 1982

Human breast epithelial cells cultured from milk have been transformed with SV40. Indirect immunofluorescence tests using monoclonal antibodies show that cells from clones grown in soft agar have SV40 large T-antigen in their nuclei and epithelia-specific tonofilament antigens on their intermediate filaments. In primary cultures of milk epithelial cells, the tono-filaments form a characteristic delicate basketwork throughout the cytoplasm, but in the SV40-transformed epithelial cell strains, the filament network is grossly distorted. Insulin, hydrocortisone, and serum stimulate the growth of the cell strains. At passages 8 to 11, the cell strains become quiescent and usually die. One cell strain survived this crisis period and gave rise to the fR series of cell lines. Most cell lines have a cuboidal morphology and react with a monoclonal antibody that recognizes a differentiation antigen on the membranes of breast epithelia. Line fR2 expressed the highest level of this antigen whereas fR5, the only fR line isolated with fusiform morphology, had relatively little. The in vitro-transformed lines may be related to the two dominant epithelial cell types seen in primary milk cultures and could be useful for studying the relationship between transformation and differentiation in human mammary epithelial cells. (Author abstract) (36 Refs)

19. HIGH-LEVEL SYNTHESIS IN ESCHERICHIA COLI OF THE SV40 SMALL-T ANTIGEN UNDER CONTROL OF THE BACTERIOPHAGE LAMBDA PL PROMOTER.

Derom C, Gheysen D, Fiers W
Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium
Gene; 17(1):45-54 1982

A series of plasmids was constructed in which the small-t gene of simian virus 40 (SV40) is under transcriptional control of the leftward promoter (pL) of bacteriophage lambda. The transcription is thermoinducible in a bacterial strain (Escherichia coli) which produces a temperature-sensitive repressor protein. Tryptic peptide analyses of the bacterial 14,500-and 19,000-dalton proteins and authentic small-t are presented. The 19,000-dalton protein was identified as a small-t antigen by specific precipitation with anti-T antiserum, coelectrophoresis on acrylamide gels with authentic small-t isolated from SV40-infected CV-1 cells, and by tryptic peptide analysis. (35 Refs)

20. SYSTEMATIC ALTERATION OF THE NUCLEOTIDE SEQUENCE PRECEDING THE TRANSLATION INITIATION CODON AND THE EFFECTS ON BACTERIAL EXPRESSION OF THE CLONED SV40 SMALL-T ANTIGEN GENE.

Gheysen D, Iserentant D, Derom C, Fiers W
Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium
Gene; 17(1):55-63 1982

In a series of recombinant plasmids which contain the simian virus 40 small-t antigen gene under control of the thermoinducible pL promoter of phage lambda, a Shine-Dalgarno ribosome-recognition (SD) sequence was created at various distances in front of the small-t translation initiation codon. In some other constructions the distance between the initiating AUG and the SD sequence was conserved while the intervening nucleotides were changed. Effects of these variables on production levels of the 19,000-dalton full-size small-t protein and on the 14,500-dalton small-t-related species are explained in terms of messenger RNA secondary structure models that could be drawn for different plasmids. (19 Refs)

21. PROPERTIES OF T ANTIGEN-POSITIVE PHENOTYPIC REVERTANTS ISOLATED FROM SV40-TRANSFORMED RAT AND MOUSE CELLS.

Maruyama K, Furuta T, Ueda K, Oda K
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Microbiol Immunol; 26(1):31-40 1982

T antigen-positive revertants isolated from SV40-transformed rat and mouse cells, which integrate six and two genome equivalents of viral DNA per cell respectively, were tested for tumorigenicity in nude mice and the relationship between tumorigenicity and karyological and growth properties of the cells was investigated. Three phenotypic revertants, R14, R15, R16, were isolated from W-3Y-23 cells. In soft agar medium, W-3Y-23 cells formed large colonies, R16 cells formed slightly smaller colonies, and neither R14 nor R15 formed large colonies. Revertant R14 showed a marked increase in the number of chromosomes to a median value of 130 and no subtetraploid cells were observed in their population. R15 and R16 showed a subtetraploid distribution similar to the parent cell line. W-3Y-23 cells were strongly tumorigenic and all the mice that received either high or low dose developed tumors within a wk. No tumors developed within 11 wk when approx 10(7) 3Y1-B, R14, or R15 cells were injected. R16 cells induced tumors that developed very slowly and became visible 8 wk after inoculation. All the tumors developed at the site of injection. R14, R15, and R16 cell DNA as well as W-3Y-23 DNA were cleaved with EcoRI which cuts the SV40 DNA once, and the DNA fragments containing the viral DNA sequence were analyzed. W-3Y-23 DNA generated seven distinct bands which were identical to those previously detected. Similar patterns were observed with all the revertant DNA; however the second and fourth bands from top of the gel were absent in all revertant DNA. In addition, the smallest band was generated from R14 and R15 DNA. The results indicate that a part of the viral DNA sequence had been deleted in all the revertants, while they still retained at least one complete viral genome. (19 Refs)

22. MICROINJECTION OF NUCLEIC ACIDS INTO CULTURED MAMMALIAN CELLS BY ELECTROPHORESIS.

Ocho M, Nakai S, Tasaka K, Watanabe S, Oda T
Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 35(5):381-384 1981

Simian virus 40 (SV40) DNA was microinjected into cultured mammalian cells by means of electrophoresis (iontophoresis). Successful transfer of DNA into cells was confirmed by detecting SV40 T antigen using the indirect immunofluorescent technique. (Author abstract) (6 Refs)

23. NONSELECTIVE EXPRESSION OF SIMIAN VIRUS 40 LARGE TUMOR ANTIGEN FRAGMENTS IN MOUSE CELLS.

Reddy VB, Tevethia SS, Tevethia MJ, Weissman SM
Southern Medical and Pharmaceutical Corporation, 3500 East Fletcher Ave., Tampa, FL, 33612
Proc Natl Acad Sci USA; 79(6,part1):2064-2067 1982

To understand the role of various functional domains of simian virus 40 early tumor antigens, we have cloned and introduced into mouse cells portions of early simian virus 40 DNA. Two types of truncated large tumor antigen (33 and 12.3 kilodaltons), as well as small tumor antigen, were identified by immunoprecipitation. Both truncated large tumor antigens have been found to be overproduced with respect to the small tumor antigen, although the 12.3-kilodalton truncated large tumor antigen was more stable than the 33-kilodalton one. Nonviral 53-kilodalton protein was not found associated with either truncated large tumor antigen in immunoprecipitations. (Author abstract) (34 Refs)

24. NUCLEOSOME SEGREGATION AT A DEFINED MAMMALIAN CHROMOSOMAL SITE.

Roufa DJ, Marchionni MA
Div. Biology, Kansas State Univ., Manhattan, KS, 66506
Proc Natl Acad Sci USA; 79(6,part1):1810-1814 1982

When animal cells replicate chromatin under conditions precluding new histone biosynthesis, half of the daughter DNAs are devoid of nucleosomes and are sensitive to staphylococcal nuclease. DNA sequences resistant to nuclease are associated with preexisting nucleosomes, which redistribute to progeny DNA duplexes during replication. We labeled newly replicated DNA sequences in a simian virus 40 (SV40)-transformed Chinese hamster cell clone with 5-bromodeoxyuridine (BrdUrd) in the presence and absence of a protein biosynthesis inhibitor,

emetine. We resolved single-stranded BrdUrd- and dT-DNA sequences protected from nuclease digestion by nucleosomes and determined from which strands of the integrated viral DNA parental template (dT) and newly replicated progeny (BrdUrd) sequences were derived. Because we knew that the cell clone studied contained all of its integrated SV40 DNA at a single chromosomal site, we were able to determine that pre-existing nucleosomes segregated to only one of the two daughter duplexes containing the integrated viral sequence. Additionally, in the presence of emetine, the integrated viral origin of replication, ORIsv, appeared not to function as a chromosomal replication origin, perhaps reflecting the drug's effect on synthesis of SV40 large tumor antigen. (Author abstract) (20 Refs)

25. CONSTRUCTION AND CHARACTERIZATION OF SV40 RECOMBINANTS WITH BETA-GLOBIN CDNA SUBSTITUTIONS IN THEIR EARLY REGIONS.

Southern PJ, Howard BH, Berg P
(c/o Berg) Dept. Biochemistry, Stanford Univ. Medical Center, Stanford, CA, 94305
J Mol Appl Genet; 1(3):177-190 1981

A complementary DNA (cDNA) segment coding for rabbit beta-globin (RBG) was inserted at three different sites in the early region of simian virus 40 (SV40). Monkey kidney cells infected with each hybrid SV40 genome produced stable, spliced polyadenylated messenger RNA (mRNA) containing the RBG cDNA sequence. Only the hybrid mRNAs containing the RBG coding sequences immediately proximal to the 5' end of the mRNA underwent translation to produce RBG. The recombinants containing the RBG coding sequence towards the 3' end of the early region yielded small t antigen and abbreviated forms of large T antigen, but little or no detectable RBG. The results suggested that the position of the RBG cDNA segment in the early region of SV40 influences the translation of the transduced coding sequences. (41 Refs)

26. ETIOPATHOGENESIS OF AVIAN MAREK'S LYMPHOMA DURING HERPES-RETROVIRUS INFECTION.

Iakovleva LS, Plakhov IV, Voronov AV, Mazurenko NP
All-Union Cancer Res. Inst., Moscow, USSR
Eksp Onkol; 4(1):18-21 1982

Interactions of Marek's disease virus (MDV) and Rous-associated virus (RAV-49) were studied in chickens. The incidence of Marek's lymphoma (ML) in chickens infected im with MDV (Group I) was 46.4%, compared with 48.4% in chickens subjected to im infection with RAV-49 and contact infection with MDV (Group II). The incidence of ML in chickens subjected to contact infection with MDV was only 14.7%. Indirect immunofluorescence showed predominance of T-cell markers in ML from Group I as well as from Group II. Analysis of MDV antigen in the epithelium of feather follicles showed the presence of virus-specific precipitating antigen starting from day 16 after im infection with MDV. In case of mixed infection, MDV antigen was first detected in 4-wk-old chickens. (18 Refs) (In RUS)

27. THE INFLUENCE OF ANTIVIRAL SERUM ON CELLS INFECTED WITH HERPES SIMPLEX VIRUS TYPE 1.

Karmysheva VYa, Rajcani J
Inst. Poliomyelitis and Viral Encephyalitides, USSR Acad. Medical Sciences, 142782 Moscow, USSR
Acta Virol (Praha); 26(1/2):79-85 1982

Homologous immune serum (IS) had an inhibitory effect on the accumulation of specific viral antigens in VERO cells infected with herpes simplex virus Type 1. When infected cells were incubated in the presence of IS, lower amounts of viral, both intracellular and membrane, antigens were found by quantitative immunofluorescence and immune cytolysis as compared to same infected cells incubated in the absence of IS. The possible mechanisms of this effect are discussed. (Author abstract) (15 Refs)

28. EXPRESSION OF HERPES SIMPLEX VIRUS TYPE-COMMON SURFACE ANTIGENS IN CLONAL CELLS OF AN HSV TYPE 2-TRANSFORMED LINE: EFFECT OF ADRIAMYCIN.

Kako D, Ohnishi Y, Kimura S
Dept. Periodontology and Endodontology, Sch. Dentistry, Tokushima Univ., Tokushima 770, Japan
Microbiol Immunol; 25(12):1265-1278 1981

The expression of herpes simplex virus (HSV) type-common surface antigen (CSA) was studied in a representative cell clone (155-4-03) of hamster cell line 155-4 transformed by HSV type 2. HSV-CSA was detected by the indirect immunofluorescence test. Expression of HSV-CSA was enhanced by treatment with inhibitors of RNA synthesis (adriamycin [ADM] and daunomycin) but not by inhibitors of DNA synthesis (2-iododeoxyuridine, bleomycin, mitomycin C and cytosine arabinoside), even though all of these agents decreased the number of viable cells in culture to about the same extent. Addition of puromycin or 2-deoxy-D-glucose to ADM markedly suppressed expression of CSA, indicating that both protein synthesis and glycosylation are necessary. ADM enhanced expression of CSA was sensitive to protease inhibitors (antipain and p-nitrophenyl-p'-guanidinobenzoate) and procaine. Procaine affects the organization of the cytoskeletal system (microfilaments and microtubules) in animal cells and also inhibits trypsin. Low concentrations of ADM (0.1 ug/ml) and actinomycin D (0.5 ug/ml) increased CSA expression in an additive manner, while optimal concentrations of each (0.25 and 2.0 ug/ml, respectively) did not. These findings indicate that the two drugs enhance CSA expression in the clone by a common mechanism. (40 Refs)

29. SULPHATED GLYCOPROTEINS INDUCED BY HERPES SIMPLEX VIRUS.

Hope RG, Palfreyman J, Suh M, Marsden HS
Medical Res. Council Virology Unit., Inst. Virology, Univ. Glasgow, Church St., Glasgow G11 5JR, Scotland
J Gen Virol; 58(part2):399-415 1982

BHK cells infected with strain 17 syn+ (HSV-1) or HG52 (HSC-2) incorporated inorganic sulfate into polypeptides which co-migrated on SDS-polyacrylamide gels with virus-induced glycoproteins. the major sulfated glycoprotein was glycoprotein E. In addition, less-intense sulfated bands co-migrated with glycoprotein D and HSV-1 glycoprotein A/B/C. Sulfate label co-migrating with HSV-2 glycoprotein A/B/C was occasionally observed. We have investigated which sulfated polypeptides are excreted from infected cells. Major ones of apparent mol wt 32,000, 34,000 and 35,000 were excreted from cells infected with 17 syn+. In addition, polypeptides which migrated in the vicinity of glycoprotein D were often excreted from cells infected with either 17 syn+ or HG52. The 32K, 34K and 35K polypeptides were antigenically related to glycoprotein D and over 95% of the total amount synthesized was excreted. Analysis of intracellular sulfated polypeptides using intertypic recombinants mapped glycoprotein E to between

0.832 and 0.950 units of the HSV genome. (Author abstract) (39 Refs)

30. A POPULATION STUDY OF HERPESVIRUS INFECTIONS AND HLA ANTIGENS.

Blackwelder WC, Dolin R, Mittal KK, McNamara PM, Payne FJ
Natl. Inst. Allergy and Infectious Diseases, NIH, Westwood Building, Room 739, Bethesda, MD, 20205
Am J Epidemiol; 115(4):569-576 1982

In a population-based study of herpesvirus infection and human leukocyte antigen (HLA) phenotype, conducted during the period 1977-1979 in the Framingham Study cohort, HLA-Bw16 was found less often and HLA-Cw2 more often in individuals with histories of herpes labialis than in other individuals. Similarly, both geometric mean antibody titer to herpes simplex Type 1 and proportion of individuals with detectable antibody were higher in those without Bw16 and in those with Cw2. No strong association was found between HLA and history of herpes zoster or titer to herpes simplex Type 2, varicella-zoster virus or cytomegalovirus. (Author abstract) (25 Refs)

31. TRANSCRIPTION OF THE HEPATITIS B SURFACE ANTIGEN GENE IN MOUSE CELLS TRANSFORMED WITH CLONED VIRAL DNA.

Pourcel C, Louise A, Gervais M, Chenciner N, Dubois MF, Tiollais P
Unite de Recombination et Expression Genetique, Institut National de la Sante et de la Recherche Medicale, U.163, Centre National de la Recherche Scientifique, LA 04271, 75724 Paris Cedex 15, France
J Virol; 42(1):100-105 1982

Mouse L cells transformed with recombinant plasmids carrying hepatitis B virus (HBV) DNA fragments were used to study the transcription of the viral surface antigen gene (gene S). An HBV-specific, polyadenylated, 2.3-kilobase RNA was mapped on the HBV genome. This RNA hybridized with approx 75% of the genome and excluded the region of the HBV core antigen gene (gene C). The 2.3-kilobase RNA species was present only in cell lines that produced hepatitis B surface antigen. An HBV-specific 2.3-kilobase RNA was also detected in human hepatoma cell line PLC/PRF/5 which produced hepatitis B surface antigen. A study of gene S expression in the transformed mouse L cells allowed us to localize the regions of initiation and termination of gene S transcription. Our results strongly suggest that the 2.3-kilobase RNA molecule is the mRNA of the major polypeptide of the envelope, which carries the viral surface antigen determinants. (Author abstract) (21 Refs)

32. AMPLIFICATION OF EXPRESSION OF HEPATITIS B SURFACE ANTIGEN IN 3T3 CELLS COTRANSFECTED WITH A DOMINANT-ACTING GENE AND CLONED VIRAL DNA.

Christman JK, Gerber M, Price PM, Flordellis C, Edelman J, Acs G
Dept. Biochemistry and Pediatrics, Mount Sinai Medical Center, New York, NY, 10021
Proc Natl Acad Sci USA; 79(6,part1):1815-1819 1982

The 3T3 cells containing hepatitis B virus DNA sequences can be efficiently selected by exposure to methotrexate after cotransfection with cloned viral DNA and DNA coding for a methotrexate-resistant dihydrofolate reductase. More than 75% of methotrexate-resistant cells isolated after cotransfection with a head-to-tail tandem of the hepatitis B virus genome synthesized viral surface antigen. The antigen was released into the culture medium in the form of 22-nm particles with buoyant density of 1.20 g/ml. No other virally coded proteins were detected in the cells or the culture medium. Application of selective pressure by increasing the concentration of methotrexate resulted in an amplification of viral DNA sequences and a concomitant increase in the rate of synthesis and release of hepatitis B surface antigen appears to be a stable trait and has been maintained in these cultures through more than 30 passages. (Author abstract) (19 Refs)

33. A MONOCLONAL ANTIBODY DEFINING A BURKITT LYMPHOMA ASSOCIATED ANTIGEN.

Wiels J, Fellous M, Lenoir G, Tursz T
Laboratoire de Immunologie, Clinique Institut G. Roussy, 94800 Villejuif, France
Protides Biol Fluid Proc Colloq; 29:899-902 1982

Reactivity of monoclonal antibody 38-13, obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma), was investigated. Negative results were obtained in all patients with B chronic lymphoid leukemia, acute lymphoid leukemia (T and nonT-nonB), acute myeloid leukemia, acute monoblastic leukemia, Hodgkin's disease, T cell lymphosarcoma, and B cell lymphosarcoma (nodular and diffuse). Positive results were observed in 4/8 patients with B cell Burkitt lymphoma. When the specific reactivity of 38.13 ascites was tested with a panel of cell lines of various origins, both by complement dependent lymphocytotoxicity tests and indirect membrane immunofluorescence assays, all the positive target cells were of Burkitt's lymphoma origin. Negative results were obtained with 15 Epstein-Barr virus positive lymphoblastoid cell lines, 4 T cell lines, a chronic myelogenous leukemia cell line, 4 teratoma cell lines, and one each of melanoma and neuroblastoma. The 38.13 monoclonal antibody may be useful for diagnosis and specific immunotherapy of Burkitt lymphomas. (8 Refs)

34. MONOCLONAL ANTIBODY AGAINST EBV-ASSOCIATED TRANSFORMATION ANTIGEN DETECTED IN VITRO AND IN VIVO.

Thorley-Lawson DA, Geilinger K, Schooley R
Div. Geographic Medicine, Tufts Univ. Sch. Medicine, Boston, MA, 02111
Protides Biol Fluid Proc Colloq; 29:739-742 1982

Transformation antigens on the surface of in vitro Epstein-Barr virus (EBV)-transformed B lymphocytes were defined by producing specific monoclonal antibodies. A hybridoma (17D6) was cloned and analyzed for its binding properties to a variety of EBV-positive and -negative B cell lines. The antibody reacted strongly with all of the EBV-positive lines and weakly with the EBV-negative lines. Similarly, a panel of EBV-negative cell lines from a variety of sources reacted only weakly with the 17D6 antibody. When a whole panel of EBV-infected cells from sources other than in vitro infection were tested, all the cell lines containing EBV were as positive as in vitro infected cells, including one cell line derived by spontaneous outgrowth from an EBV-positive individual and one from co-cultivation of normal lymphocytes from a seronegative individual with a nasopharyngeal carcinoma. Burkitt's lymphoma tumor cells reacted only weakly with the 17D6 antibody due to their relatively low levels of the antigen. 17D6-positive cells also were detected in the peripheral blood of infectious mononucleosis (IM) patients. 17D6-positive cells could be detected in the peripheral blood of a patient with chronic EBV infection at higher levels than in patients with acute IM. After recovery, no 17D6-positive cells could be detected.

Radioimmunoprecipitation studies suggested that the 17D6 antibody recognizes a polypeptide of 40,000 mol wt. The results indicated that the 17D6 antibody recognizes an EBV-associated transformation antigen on the surface of in vitro and in vivo infected cells. (4 Refs)

35. TWO DISTINCT HUMAN CLONED T CELL LINES THAT EXHIBIT NATURAL KILLER-LIKE AND ANTI-HUMAN EFFECTOR ACTIVITIES.

Sugamura K, Tanaka Y, Hinuma Y
Inst. Virus Res., Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
J Immunol; 128(4):1749-1752 1982

Cloned T cell lines from mixed lymphocyte cultures stimulated with autologous Epstein Barr virus- (EBV) transformed lymphoblastoid cell line (LCL) cells were established using a limiting dilution technique in the presence of T cell growth factor (TCGF). The T cell lines included two distinct clones of cytotoxicity T cells (Tc) in addition to EBV-specific Tc. A cytotoxic profile of one cloned line was similar to that of endogenous NK cells in peripheral blood. The other cloned Tc line showed an anti-human cytotoxicity. The susceptible targets for this latter Tc line were various human cells, including autologous LCL and peripheral blood lymphocytes (PBL), stimulated with pokeweed mitogen, along with NK-sensitive and NK-resistant cell lines. Weak cytotoxic activity was detected against various xenogeneic cell lines. Furthermore, autologous and allogeneic cloned T cell lines were resistant to killing by the anti-human effector clone. These two distinct cloned Tc lines expressed the Leu-1 and Leu-2a antigens, which are markers of suppressor/cytotoxic T cells. (Author abstract) (23 Refs)

36. MIGRATION INHIBITION CAUSED BY EBV-SPECIFIC 48K SUBCOMPONENT OF EBNA AND THE ASSOCIATED 53K CELLULAR PROTEIN.

Szigeti R, Luka J, Sternas L, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Int J Cancer; 29(4):413-416 1982

Leukocytes from EBV-seropositive but not seronegative healthy donors responded with significant migration inhibition to the 48K subcomponent of the Epstein-Barr virus determined nuclear antigen (EBNA), known to carry the virally determined antigenic specificity. A concentration of 10 ug/ml was still effective while 5 ug/ml had no detectable effect. EBNA-associated cellular 53K protein had no effect by itself, but it potentiated the effect of 48K, even if the latter was added at the subliminal concentration of 5 ug/ml. The related 53K protein, isolated from EBV-negative human lymphoma cells, was also effective, whereas the corresponding murine-tumor-associated 53K had no potentiating effect. Immunization of mice with an extract of DNA-binding proteins from EBV-carrying Raji cells, known to contain both 48K and 53K, induced a significant macrophage migration inhibition response, to both human 48K and 53K. Murine 53K was ineffective, however. Human but not murine 53K increased the migration inhibitory activity of subliminal concentrations of 48K in the murine macrophage system as well. These findings suggest that human but not murine 53K may reconstitute with 48K (EBNA) to form a highly immunogenic complex. (Author abstract) (24 Refs)

37. SPONTANEOUS INTERFERON PRODUCTION AND GROWTH OF LYMPHOBLASTOID CELLS IN SERUM-FREE MEDIUM.

Sato T, Minamoto Y, Yamane I, Kudo T, Tachibana T
Dept. Cell Biology, Res. Inst. Tuberculosis and Cancer, Tohoku Univ., Sendai 980, Japan
Exp Cell Res; 138(1):127-134 1982

Numerous lymphoblastoid cell lines were established from human adult peripheral blood and cord blood lymphocytes, using Epstein Barr virus, and most cell lines from cord blood lymphocytes spontaneously produced abundant interferon without induction with Sendai virus, whereas lymphoblastoid cells from adult peripheral blood lymphocytes did not. these potential cells grow well in a newly developed serum-free culture medium based on Dulbecco's modified Eagle medium supplemented with non-essential amino acid, vitamins, nucleic acid derivatives, metal compounds, human transferrin, insulin and bovine or human serum albumin (Chon Fr V). In serum-free medium, as well as in serum-containing conventional medium (RPMI-1640), the cells could also spontaneously produce interferon. The cells in the serum-free culture could produce about 10,000 U/ml of interferon every day, harvesting the culture fluid and refeeding the cells with the fresh medium at the saturation cell density (10(7) cells/ml). The interferon proved to be alpha-type interferon on the basis of its physicochemical and antigenic properties. (Author abstract) (32 Refs)

38. WHAT DO B LYMPHOCYTES AND NASOPHARYNGEAL EPITHELIUM HAVE IN COMMON?

North JR
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Immunol Today; 2(12):232-233 1981

The mechanism of Epstein-Barr virus (EBV) entry into nasopharyngeal epithelial cells is unknown. Evidence is presented demonstrating that of the cell types known to support expression of the EBV genome, only human and marmoset B lymphocytes and a squamous epithelial cell subset residing in the human nasopharynx are immortalized and express Epstein-Barr nuclear antigen. The common denominator between the cell types remains to be determined. (11 Refs)

39. LONG-TERM HUMAN CYTOLYTIC T-CELL LINES ALLOSPECIFIC FOR HLA-DR6 ANTIGEN ARE OKT4+.

Krensky AM, Reiss CS, Mier JW, Strominger JL, Burakoff SJ
Sidney Farber Cancer Inst., Children's Hosp. Medical Center, Boston, MA, 02115
Proc Natl Acad Sci USA; 79(7):2365-2369 1982

Human allospecific cytotoxic T lymphocyte lines were established by weekly stimulation of peripheral blood lymphocytes with allogeneic Epstein-Barr virus-transformed lymphoblastoid cell lines in the presence of interleukin 2. The cytotoxic T lymphocyte lines were stimulated by either JY (which expresses HLA-A,B and -DR) or Daudi (which expresses HLA-DR but not -A,B antigens). Specificity of the effector cell lines was determined by antibody blocking and by patterns of cytolysis against a panel of target cell lines. The phenotype of the effector cells was identified by both negative (antibody and complement lysis) and positive (fluorescence-activated cell sorter) selection. The anti-JY lines only recognized targets bearing HLA-A2 or B7 antigens and were composed exclusively of OKT4-8+ effector cells. The anti-Daudi lines, on the other hand, specifically recognized targets bearing DR6 and eventually contained only OKT4+8-cells. Thus, stimulation by Daudi

cells can result in the generation of OKT4+ CTL lines that are allospecific for DR6 antigen. (Author abstract) (34 Refs)

40. MONOCLONAL ANTIBODIES DETECTING EPSTEIN-BARR VIRUS STRAIN AND GROUP SPECIFIC ANTIGENIC DETERMINANTS.

Herbst H, Georg-Fries B, Muller-Lantzsch N, Hausen HZ, Braun DG
Pharmaceuticals Res. Div., CIBA-GEIGY, Basel, Switzerland
Protides Biol Fluid Proc Colloq; 29:735-738 1982

The ability of monoclonal antibodies to detect common and group- and strain-specific antigenic sites on Epstein-Barr virus (EBV) proteins was examined. The EBV strain QIMR-WIL expressing four major envelope polypeptides of mol wt 80,000 (p80), 140,000 (p140), 240,000 (p240), and 340,000 (p340) was used for immunization. Ten of 144 culture supernatants exhibited clearly positive reactions, while 21 gave a weak immunofluorescence. One culture fluid precipitated polypeptide p80 exclusively, while others after cloning precipitated selectively p140, p340, or p240/p340 in combination. Cross-reactions with corresponding polypeptides of EBV strains P3HR-1 and B95-8 were studied. It was suggested that monoclonal antibodies can provide a serological basis for EBV typing. (9 Refs)

41. THE STRUCTURE AND FUNCTION OF A MEMBRANE GLYCOPROTEIN ENCODED IN THE ADENOVIRUS GENOME.

Persson H, Philipson L
Dept. Microbiology, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden
Protides Biol Fluid Proc Colloq; 29:97-100 1982

A glycoprotein encoded in the adenovirus genome interacts with the heavy chain of transplantation antigens. Sequence analysis of the E3/16,000 mol wt precursor protein obtained from adenovirus messenger RNA revealed a signal sequence in the N-terminal end and a hydrophobic sequence in the C-terminal end. Two sites are available for addition of carbohydrate to the side chains. It is now possible to identify the region which specifically interacts with HLA in human cells. (5 Refs)

42. ANTIBODIES CONJUGATED TO POTENT CYTOTOXINS AS SPECIFIC ANTITUMOR AGENTS.

Moolten FL, Schreiber BM, Zajdel SH
Boston Univ. Sch. Medicine, Boston, MA
Immunol Rev; 62:47-73 1982

The ability of toxins, enzymes, radioisotopes, and cytotoxic drugs linked to antibodies to selectively kill cells bearing surface antigens that are targets for the antibodies is reviewed. Criteria for the complexes include the following: the cytotoxin must be capable of acting after delivery to the cell surface by the antibody, the desired biologic properties of the components must survive the conjugation process, the conjugate must be stable until delivered to its site of action, the specificity of the conjugate must reflect primarily the specificity of the antibody complex, and the toxic moiety must be extraordinarily potent. Conjugates tested for antitumor activity include diphtheria toxin conjugates, Pseudomonas aeruginosa toxin conjugates, ricin conjugates, and phospholipase and ribonuclease conjugates. In vitro, each of the agents, when conjugated to antibodies directed against a variety of cell-surface antigens, was selectively cytotoxic to cells bearing those antigens. In vivo, diphtheria toxin conjugated to antibodies directed against the dinitrophenol (DNP) hapten reduced the incidence and growth rate of tumors in hamsters concurrently inoculated with DNP-coated sarcoma cells. When tested against a more sensitive Simian virus 40-induced tumor, two conjugate preparations induced permanent regressions of established tumor in 20% and 56% of treated hamsters. (65 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

43. RADIOIMMUNOLOCALIZATION OF MURINE MAMMARY TUMOR VIRUS PROTEINS IN GELS.

Bausch JN, Prasad KS, Spiegelman S
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Anal Biochem; 119(2):293-298 1982

A procedure for the immunological detection of antigens on sodium dodecyl sulfate-polyacrylamide gels using iodinated antibodies combined with an immunoconcentration step to enrich for the desired antigen(s) is described. This selective enrichment is achieved by separation of the antigen-antibody complexes with formalin-treated cells of Staphylococcus aureus and is followed by radioimmunolocalization on gels. This method is particularly useful for the characterization of antigens present at low concentrations in complex biological fluids. Its usefulness is exemplified here by the successful identification of mouse mammary tumor virus antigens in extracts of murine mammary tumors and in plasmas of tumor-bearing animals. In particular, the procedure permits the ready determination that the gp52 protein detected in the plasmas of tumor-bearing animals is in fact present as a 52,000-dalton species and not as a higher mol wt precursor. (Author abstract) (17 Refs)

44. INTRACELLULAR LOCALIZATION OF CERTAIN MEMBRANE GLYCOPROTEINS IN MOUSE T-LYMPHOMA CELLS USING IMMUNOFERRITIN STAINING OF ULTRATHIN FROZEN SECTIONS.

Bourguignon LY, Butman BT
Dept. Anatomy, Sch. Medicine, Univ. Miami, Miami, FL, 33101
J Cell Physiol; 110(2):203-212 1982

Morphology observed with frozen thin sections of mouse T-lymphoma cells was compared with that of epon thin sections, with special emphasis on membranous organelles. The intracellular localization of several types of membrane glycoproteins in the T-lymphoma cell system was examined. No significant differences were found between epon and frozen thin sections. Immunoferritin staining on frozen thin sections was specific, reliable, and suitable for intracellular localization of various membrane glycoproteins based on studies using antibodies directed against Thy-1, a T-cell-specific membrane glycoprotein. Many of the membranous cellular structures of the T-lymphoma cells contained the concanavalin A-specific sugars, alpha-D-mannose and alpha-D-glucose. The intracellular distribution of the viral membrane protein, gp 69/71, was studied in lymphoma cells known to be productively infected with a C-type RNA virus. Gp 69/71 molecules were detected on the surface of free and budding C-type viral particles. Occasionally, gp 69/71 was also found in discontinuous patchlike arrays along certain regions of the T-lymphoma cell surface. Viral antigens were found in terminal regions of certain flattened rough endoplasmic reticulum membranes, in a diffuse pattern at certain regions of the stacked Golgi membranes, and in clustered arrays within small vesicle-like structures either close to the plasma membrane or at an apparent point of contact be-

tween an individual vesicle and the plasma membrane. (19 Refs)

45. PROTEINS ANTIGENICALLY RELATED TO THE HUMAN ERYTHROCYTE GLUCOSE TRANSPORTER IN NORMAL AND ROUS SARCOMA VIRUS-TRANSFORMED CHICKEN EMBRYO FIBROBLASTS.

Salter DW, Baldwin SA, Lienhard GE, Weber MJ
Dept. Microbiology and Public Health, Michigan State Univ., East Lansing, MI, 48823
Proc Natl Acad Sci USA; 79(5):1540-1544 1982

Antibody raised against the purified human erythrocyte glucose transporter specifically precipitated four proteins from normal and Rous sarcoma virus-transformed chicken embryo cells: a major protein of Mr 41,000 and minor proteins of Mr 68,000, 73,000, and 82,000. The Mr 41,000 and 82,000 proteins were found only in a membrane fraction, not in the soluble fraction, and displayed a heterogeneous mobility on NaDodSO4/polyacrylamide gel electrophoresis, suggesting glycosylation. The Mr 41,000 and 82,000 proteins were increased in amount after malignant transformation in direct proportion to the increase in hexose transport rate, and the increase was dependent on the expression of the src gene product, as revealed with a temperature-conditional src mutant. We suggest that the Mr 41,000 and 82,000 proteins are the glucose transporter of chicken embryo fibroblasts, or a component of the glucose transporter. These experiments provide direct evidence that malignant transformation increases the rate of glucose transport by increasing the number of transporters in the membrane. (Author abstract) (27 Refs)

46. DISSECTION OF THE ANTIGENIC DETERMINANTS EXPRESSED ON THE CELL SURFACE OF RSV-TRANSFORMED FIBROBLASTS BY MONOCLONAL ANTIBODIES.

Ferracini R, Prat M, Comoglio PM
Univ. Trieste, Sch. Medicine, Trieste, Italy
Int J Cancer; 29(4):477-481 1982

Fusion of P3/X63-Ag8 mouse myeloma cells with splenocytes obtained from mice hyperimmunized with a BHK hamster fibroblast line transformed by an env-strain of Rous sarcoma virus (RSV) resulted in the production of antibody-secreting hybridomas. Seven hybrid clones secreted antibodies binding to RSV-transformed BHK fibroblasts but not to the parental control non-transformed line. The antibodies produced by three of these clones did identify antigenic determinants expressed also on BHK cells transformed by SV40. The antibodies produced by four other clones reacted specifically with cells transformed by RSV but not with cells productively infected by the transformation-defective Rous-associated virus-I; one of these reacted with RSV-transformed hamster cells only, three others identified antigenic determinants common to RSV-transformed cells of different animal species. These data give further support to the idea that RSV-transformed cells express a cell-surface antigen, specific for transformation, the expression of which is controlled by the transforming src gene, and that the specificities carried on it follow a complex pattern, arising from the interaction between antigenic determinants of cellular and viral origin. (Author abstract) (49 Refs)

47. ERADICATION OF BOVINE LEUKEMIA VIRUS INFECTION FROM A HIGH-PREVALENCE HERD, USING RADIOIMMUNOASSAY FOR IDENTIFICATION OF INFECTED ANIMALS.

Ferrer JF
Section Viral Oncology, Comparative Leukemia Studies Unit, Sch. Veterinary Medicine, Univ. Pennsylvania, New Bolton Center, Kennett Square, PA, 19348
J Am Vet Med Assoc; 180(8):890-893 1982

Radioimmunoassay (RIA), using the virion glycoprotein antigen, was applied in an attempt to eradicate bovine leukemia virus (BLV) infection from a herd in which virtually all the adult cattle are infected. Considering that most calves born to BLV-infected cows are negative for BLV at birth and remain negative for the first several mo of life, the eradication program was based on the identification and isolation of the BLV-free calves born to infected cows. Twenty-five calves raised on colostrum and milk from their infected dams were classified as BLV-free on the basis of negative results in the RIA at 6 to 8 and 9 to 11 mo of age. These animals were maintained in either complete (10 calves) or partial (15 calves) isolation from infected cattle and were examined at regular intervals for BLV and BLV antibodies. With the exception of one calf in the group raised in partial isolation, the animals have remained free of BLV up to the time of the last evaluation, when they were 32 to 35 mo old. At these ages, more than 90% of the nonisolated cattle in the herd are BLV-positive. The data also show that this eradication trial would have failed if in the initial procedure used to classify the calves as BLV-free, the agar gel immunodiffusion test instead of the RIA had been used. Inasmuch as the 25 calves in this study were fed colostrum and milk from their dams, the fact that only 1 of the calves became infected during the 26 to 29 mo of observation provides further evidence that milk-borne transmission of BLV is infrequent and perhaps inconsequential. (Author abstract) (32 Refs)

48. AN IGM-PRODUCING B LYMPHOBLASTOID CELL LINE ESTABLISHED FROM LYMPHOMAS INDUCED BY A NON-DEFECTIVE RETICULOENDOTHELIOSIS VIRUS.

Nazerian K, Witter RL, Crittenden LB, Noori-Dalloii MR, Kung HJ
Regional Poultry Res. Lab., U.S. Dept. Agriculture, 3606, East Mount Hope Road, East Lansing, MI, 48823
J Gen Virol; 58(part2):351-360 1982

Chick syncytial virus (CSV), a strain of avian reticuloendotheliosis virus (REV) causes lymphoid tumors in chickens after a prolonged incubation period. A number of CSV-induced tumors were examined for cell surface antigen and were found to be of the B cell type and to produce immunoglobulin. Attempts were made to grow in vitro cell lines from CSV-induced tumors and a lymphoblastoid cell line was established from a liver tumor of a chicken that was inoculated with CSV via the yolk sac in embryo. The donor chicken was viremic at the time the tumor was removed. The cell line is designated RECC-RP13, it produces non-defective REV, is a B cell type and it produces IgM. It is free from infection with endogenous and exogenous avian leukosis virus (ALV) and has an increased number of chromosomes. Sequences specific to REV were detected in at least four sites in cellular DNA from RECC-RP13. Sequences specific to ALV DNA, beyond that normally found in 1515 x 71 cells, were not found in DNA from this cell line. (Author abstract) (31 Refs)

49. COMPLETE AMINO ACID SEQUENCE OF THE GROUP-SPECIFIC ANTIGEN GENE-ENCODED PHOSPHORYLATED PROTEINS OF MOUSE LEUKEMIA VIRUSES.

Versteegen RJ, Copeland TD, Oroszlan S
Biological Carcinogenesis Program, Frederick Cancer Res. Facility, Frederick, MD, 21701
J Biol Chem; 257(6):3007-3013 1982

The complete amino acid sequence of the group-specific antigen gene-encoded RNA binding phosphoprotein p12 has been determined for both Rauscher and Moloney leukemia viruses. Large fragments generated by acid, cyanogen bromide and hydroxylamine cleavage, and Staphylococcus aureus V8 protease digestion were subjected to automated sequencing. Both Rauscher and Moloney p12 are composed of 84 amino acids arranged in alternating variable and conserved regions. The homology between the conserved internal and COOH-terminal regions is greater than 95%, but the NH2-terminal and internal variable regions show 59 and 51% homology, respectively. The role of such regions in the type-specific biological activities of these molecules is discussed. (Author abstract) (42 Refs)

50. SEARCH FOR RETROVIRUS EXPRESSION IN MEN - FAILURE TO DEMONSTRATE RETROVIRUS-SPECIFIC ANTIGENS IN NORMAL AND MALIGNANT TISSUE.

Micheel B, Wunderlich V, Hertling I
Zentralinstitut fur Krebsforschung, Lindenberger Weg 70/80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(3):169-173 1982

Immunological experiments using the Sepharose bead immunofluorescence assay to demonstrate retrovirus antigens in different human tissues are presented. With some of the extracts (in particular from placentas and leukemic tissues) slightly positive reactions were observed, especially in the interspecies-specific type C virus assay. An unequivocally positive result could not be obtained in any case. With some samples, the test was negative when repeated, with others the values were just at the significance border and turned out to be insignificant when the competition by uninfected cellular extracts was taken as a reference. Results indicated that a virus specificity was nonexistent. (17 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

51. COMPLEMENTATION OF MAJOR HISTOCOMPATIBILITY HAPLOTYPES IN REGRESSION OF ROUS SARCOMA VIRUS-INDUCED TUMORS OF NONINBRED CHICKENS.

Brown DW, Collins WM, Ward PH, Briles WE
Dept. Animal Sciences, Univ. New Hampshire, Durham, NH, 03824
Poult Sci; 61(3):409-413 1982

Relative responses to Rous sarcoma virus (RSV)-induced tumors were studied in noninbred UNH 105 chickens. Chickens were blood typed for B alloantigens at 4 wk of age, and three homozygous genotyes (B23/B23, B24/B24, and B26/B26) and three heterozygous genotypes (B23/B24, B23/B26, and B24/B26) were studied. Chicks were inoculated with 0.1 ml of RSV (approx 20 pock-forming units) at 6 wk of age. A tumor profile index (TPI) was assigned to each chicken. Tumors developed in 795 chickens. Of B23/26 chickens, 54% were regressors compared with 34% of B23/B23 and 26% of B26/B26. The greatest incidence of tumor progression occurred in B24/B24 chickens (87%) in contrast to 23% in B23/B26 chickens. The homozygous genotypes had mean TPIs of 2.0-2.9 which were significantly different from each other. The greatest antitumor response was observed when the B23 and B26 haplotypes were combined; however, when B24 was combined with either B23 or B26, antitumor response was smaller than that observed for homozygotes of B23 or B26. The number and mean TPI of progeny from various kinds of matings were determined; the antitumor response of B23/B26 chickens was greater than that of the B23/B23 and B26/B26 chickens. These results suggest complementation of haplotypes influencing the anti-Rous sarcoma response. (19 Refs)

52. IMMUNE SELECTION OF TUMOR CELL VARIANTS IN CHICKENS BEARING TUMORS INDUCED BY AVIAN SARCOMA VIRUS.

Wainberg MA, Israel E, Yu M
Lady Davis Inst. for Medical Res., Sir Mortimer B. Davis-Jewish General Hosp., Montreal, H3T 1E2 Quebec, Canada
Cancer Res; 42(5):1669-1675 1982

We have compared avian sarcoma cells, cultured from tumors at various stages of growth, in terms of their ability to synthesize infectious progeny virus and to express antigens that are reactive with the sensitized lymphocytes of tumor-bearing host. Cell-mediated immunity in chickens bearing tumors induced by avian sarcoma viruses was monitored by each of a target cell cytotoxicity test and an antigen-driven lymphocyte stimulation assay. Our results show that it is only those tumor cells which have been derived from progressively growing neoplasms that are able to synthesize infectious progeny virus and to specifically interact with the sensitized lymphocytes of tumor-bearing hosts. In contrast, cells from regressing tumors do not express relevant antigens to the same extent as do progressors, and they synthesize noninfectious particles only. Experiments on cellular outgrowths, derived from the plating at limited dilution of progressively growing tumor cells, revealed that such producers of defective virus are present at the earliest stages of tumor growth. Both these cells and regressing tumor cells are poorly stained (about 10%) in indirect immunofluorescence tests by antiserum against viral envelope glycoprotein, whereas tumor cell from progressing neoplasms react well (about 60 to 85%). These results suggest that tumor cells which are found in regressing neoplasms are selected out by a functional immune response directed against cells which are efficient producers of progeny virus. (Author abstract) (24 Refs)

53. THE EFFECTS OF T-CELL GROWTH FACTOR AND VIRUS PURIFICATION ON VIRUS-MEDIATED INHIBITION OF LYMPHOCYTE MITOGENESIS.

Wainberg MA, Margolese RG
Lady Davis Inst. Medical Res., Sir Mortimer B. Davis - Jewish General Hosp., 3755 Cote St. Catherine Road, Montreal, Quebec H3T 1E2, Canada
Clin Exp Immunol; 48(1):163-170 1982

Many different types of virus particles are able to non-specifically impede the ability of human peripheral blood lymphocytes to respond to mitogenic or alloantigenic stimuli. This result is not obtained if ultra-purified virus is employed, although virus which has been banded only once through sucrose generally retains inhibitory potential. Ultra-pure virus is relatively unable to bind to cell surfaces, suggesting the impor-

tance of physical contact between viruses and cells in order for the observed inhibition to occur. Addition of exogenous T-cell growth factor (TCGF) to cultures containing virus, cells and stimulus causes a dose-dependent reversal of the usual inhibitory effect. (Author abstract) (34 Refs)

54. INCREASED OR DECREASED IMMUNOGENICITY OF TUMOR-ASSOCIATED ANTIGEN ACCORDING TO THE AMOUNT OF VIRUS-ASSOCIATED ANTIGEN IN RAT TUMOR CELLS INFECTED WITH FRIEND VIRUS.

Yamaguchi H, Moriuchi T, Hosokawa M, Kobayashi H
Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060, Japan
Cancer Immunol Immunother; 12(2):119-123 1982

Grading of tumor-associated antigen (TAA) is described with particular reference to the amount of virus-associated antigen (VAA) newly produced by non-lytic virus infection. Complement-dependent cytotoxic sensitivity of Friend virus (FV)-KMT-17 rat fibrosarcoma cells to anti-VAA serum increased proportionally following serial passage generations with a max at passage 6. The absorbing capacity potentials for removing 50% of anti-VAA serum activity were 12.0x higher in FV-KMT-17 (F6), and 3.2x higher in FV-KMT-17 (F4) cells than in FV-KMT-17 (F2) cells. No difference in absorbing capacities of FV-KMT-17 (F0, 2, 4, and 6) for anti-TAA serum were observed. When WKA/Hok rats were immunized with FV-KMT-17 (F2, 4, 6 and 0) cells having various amounts of VAA and subsequently challenged with 10(5) or 10(6) viable KMT-17 cells, survival rates of 20.8%, 83.3%, 18.2% and 45.8%,respectively, were obtained. Immunization of FV-tolerant rats with FV-KMT-17 (F2, 4, and 6) cells resulted in similar levels of transplantation resistance without marked difference from the non-passage F0. Immunization of normal rats with a mixture of WLFT-6 rat thymoma cells [1.6 x 10(7) possessing an amount of VAA almost equivalent to that in FV-KMT-17 (F4)] and 5.0 x 10(7) KMT-17 cells resulted in lower transplantation resistance than for FV-KMT-17 (F4) cells alone, suggesting that VAA and TAA must be present on the same cell. The results indicated that TAA immunogenicity increases when an appropriate amount of VAA is expressed on the tumor cell surface and decreases when a relatively low or excessive amount of VAA is expressed. (22 Refs)

55. INFLUENCE OF SELECTIVE ABSENCE OF H-2KKAPPA ON GROSS VIRUS LEUKAEMIAS IN VITRO AND THE IMPLICATIONS FOR IN VIVO SURVEILLANCE OF LEUKAEMIA.

Festenstein H, Schmidt W, Alonzo A, Leben L
Dept. Immunology, London Hosp. Medical Coll., London, England
Protides Biol Fluid Proc Colloq; 29:231-235 1982

Results are presented of direct complement dependent cytotoxicity tests using anti H-2Kkappa (H-2Kk) monoclonal antibody on five primary AKR leukemias. These and earlier results permit the conclusion that the absence/reduction of the H-Kk gene product is not uncommon in Gross virus leukemia. In search of the biological implication of this finding, a comparison was made of the ability of the K-GV BALB/c Gross virus tumor, which lacks Kk, and other Gross virus tumors with normal H-2Kk representation, to act as targets in cell mediated lympholysis (CML). Results showed that resistance to syngeneic CML is apparently due to the absence of Kk and is thus a failure of associative recognition. Results suggest a new mechanism of escape of T cell surveillance by leukemic cells which involves selective decrease of the H-2Kk antigens, which in this and other studies, have been shown to serve as elements of associative recognition in Gross virus leukemia. (6 Refs)

56. IMPAIRMENT OF SPLENIC NATURAL KILLER CELL ACTIVITY OF MICE INFECTED WITH THE POLYCYTHEMIC STRAIN OF FRIEND LEUKEMIA VIRUS.

Migliorati G, Jezzi T, Favalli C, Garaci E, Rossi RB, Bonmassar E
Inst. Pharmacology, Univ. Perugia, via del Giochetto, I-06100 Perugia, Italy
Cancer Immunol Immunother; 12(2):177-179 1982

The effect of polycythemic strain Friend leukemia virus (FLV-P) infection on natural killer (NK) activity in FLV-P susceptible DBA/2 inbred mouse recipients was examined. Spleen cells were collected from 4-wk-old control or FLV-P-infected donors on days 2, 7, 14, 21, and 28 after virus inoculation. Pools of four spleens each were tested for NK activity at various attacker:target ratios. A significant decrease of NK activity occurred as early as 7 days after infection. From day 14 onward, splenic NK function of infected mice was minimal. Moreover, an actual decrease of NK activity of the whole spleen occurred in these mice, as evidenced by the extremely low levels of lytic units per spleen detectable 3 wk after FLV-P infection. A limited but progressive decline of NK activity was found in the spleen of control non-infected donors, presumably expressing an age-dependent decrease of NK levels in the organ. The mechanism of suppression is discussed. It was suggested that suppression could be based on cell-mediated impairment of NK effector function, or on antigenic competition from splenocytes expressing NK antigens elicited by FLV-P. (19 Refs)

57. SPECIFICITY STUDIES OF CYTOLYTIC T LYMPHOCYTES DIRECTED AGAINST MURINE LEUKEMIA VIRUS-INDUCED TUMORS. ANALYSIS BY MONOCLONAL CYTOLYTIC T LYMPHOCYTES.

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Unite d'Immuno-Parasitologie, Institut Pasteur, 25 rue du Docteur Roux, 75015 Paris, France
J Exp Med; 155(4):1050-1062 1982

Specificities of cloned cytolytic T lymphocytes (CTL) were investigated for the analysis of CTL populations generated against murine leukemia viruses (MuLV) in H-2 congenic BALB/c (H-2d) and BALB.B (H-2b) mice. CTL elicited by immunization with syngeneic Friend or Gross MuLV-induced tumors in these mice were studied. Optimal conditions for proliferation and long-term culture of MuLV-specific CTL were determined. Ninety-two lymphocyte clones were assayed independently on a panel of 51Cr-labeled tumor target cells. Clones were then distributed into different groups according to their specificities. Most of the CTL clones (52-64%) attacked the tumor cell against which they were initially primed and not any of the other tumor cells assayed. Other clones were specific for the priming MuLV-induced antigen in apparent association with an H-2 public specificity shared between H-2b and H-2d antigens (5-16%); were specific for tumor cells induced by Gross, Rauscher, Friend, and Moloney MuLV and were H-2 restricted (6 clones); was H-2b restricted and recognized only RBL-5 and HFL/b tumor cells of the Friend, Moloney, or Rauscher family (1 clone); showed a total lack of target specificity (21 clones); or lacked detectable cytotoxic activity (2 clones). Thus, the highly heterogeneous constitution of CTL populations generated against MuLV-induced tumors in BALB/c and BALB.B mice was demonstrated. (40 Refs)

58. INFLUENCE OF H-2-LINKED GENES ON T CELL PROLIFERATIVE AND CYTOLYTIC RESPONSES TO PEPTIDES OF SENDAI VIRAL PROTEINS.

Mitkimen JA, Guertin DP, Fan DP, David CS
Dept. Microbiology, Univ. Minnesota, Minneapolis, MN, 55455
J Immunol; 128(4):1522-1528 1982

Spleen cells from H-2 congenic mice were tested for their proliferative and/or cytolytic responses to partially purified products from CNBr cleavage of Sendai virus. In response to in vitro stimulation of Sendai-primed spleen cells with virus-infected cells, Sendai virus-specific cytolytic T lymphocytes restricted to H-2Kb, Kd, Kk, Ks, and Dd were generated. Of these H-2Kb- and Kd-, but not H-2Kk-, Ks-, and Dd-, restricted cytolytic T cells were generated after stimulation with partially purified Sendai peptides. H-2Dd-restricted, virus-specific cytotoxicity was generated in response to unseparated products from CNBr cleavage of Sendai virus. The pool of partially purified peptides contains some of the antigenic determinants that can stimulate a cytolytic response. These results suggest that each determinant on Sendai viral proteins may stimulate cytolytic T lymphocytes restricted to only a subset of the H-2K and D alleles which can be recognized by the sum of cytolytic T cells generated in response to all of the antigenic determinants on Sendai viral proteins. Thus, H-2K and D genes function as immune response genes regulating the cytolytic response to partially purified peptides and possibly to individual antigenic determinants on Sendai viral proteins. Only spleen cells from mice with the k haplotype in IA-IJ proliferate in response to partially purified peptides, whereas spleen cells from all three mice proliferate when virus is added to the cultures. These proliferating cells are sensitive to treatment with anti-Thy-1.2 and C, suggesting that immune response genes regulating T cell proliferative responses to individual viral determinants may also exist. (14 Refs)

59. SPLIT T-CELL TOLERANCE IN HERPES SIMPLEX VIRUS-INFECTED MICE AND ITS IMPLICATION FOR ANTI-VIRAL IMMUNITY.

Nash AA, Ashford NP
Dept. Pathology, Univ. Cambridge, Tennis Court Road, Cambridge, England
Immunology; 45(4):761-767 1982

Mice simultaneously injected intravenously and subcutaneously with herpes simplex virus fail to adoptively transfer delayed hypersensitivity (DH) to syngeneic recipients. The transferred lymph node cells also failed to rapidly eliminate infectious herpes from the pinna, despite the presence of cytotoxic T cells in the transferred suspension. Both primary and secondary cytotoxic cell responses in the draining lymph node were unaffected by the inhibition of DH. The lymph nodes from DH tolerized mice also contain lymphocytes capable of undergoing a proliferative response in vitro to herpes antigens. In addition, a neutralizing antibody response with IgG antibodies against herpes are also present in DH tolerized mice. These data suggest a form of split T-cell tolerance in which only DH responses are directly compromised. The implication of these findings for the pathogenesis of herpes simplex virus is discussed. (Author abstract) (13 Refs)

60. EPSTEIN-BARR VIRUS INCREASES THE PROLIFERATIVE RESPONSE AND THE GENERATION OF SUPPRESSOR AND CYTOTOXIC T-CELL FUNCTIONS IN AUTOLOGOUS MIXED LYMPHOCYTE REACTION.

Palacios R
Dept. Immunobiology, Wallenberg Lab., Karolinska Inst., S-104 05 Stockholm, Sweden
Scand J Immunol; 15(1):17-24 1982

Epstein-Barr virus (EBV) infection of stimulator cells significantly increased the proliferative response of T cells in the autologous mixed lymphocyte reaction (AMLR). The addition of a monoclonal anti-HLA-DR antibody to AMLR cultures in which either EBV-infected or non-infected non-T cells were used as stimulator cells strongly inhibited the proliferative response irrespective of the presence of EBV. It is concluded that EBV does not by itself activate the responding cells and that HLA-DR antigens are necessary to trigger T cells. Increased generation of suppressor T cells, determined in both alloantigen-induced DNA synthesis and pokeweed-mitogen-stimulated immunoglobulin production, was found after an EBV infection of stimulator cells. Similarly, EBV-infected non-T cells significantly increased the generation of killer T cells, determined in three different types of target cells: phytohemagglutinin-stimulated mononuclear cells, EBV-transformed cells, and concanavalin-A-activated murine spleen cells. The increased T-cell responses after an EBV infection may reflect the attempts in vivo to control and hold in check the viral infection. (Author abstract) (33 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

61. EFFECT OF PROSTAGLANDINS ON ELICITATION OF ANTI-VIRAL CYTOLYTIC ACTIVITY.

Hale AH, Evans DL, Daniel LW
(c/o Daniel) Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103
Immunol Lett; 4(3):171-174 1982

The modulating effect of prostaglandins (PG) E1 and E2 on the elicitation of secondary anti-vesicular stomatitis virus (VSV) cytotoxic T-lymphocytes (CTL) with viral antigens was studied. Results indicate both PGE1 and PGE2 inhibit induction of anti-VSV CTLs by UV-inactivated VSV. In the presence of indomethacin, VSV CTL activity was augmented. Results suggest prostaglandins may modulate anti-viral CTL responses. (16 Refs)

62. INTERVENING EFFECT OF L-ASCORBIC ACID ON EPSTEIN-BARR VIRUS ACTIVATION IN HUMAN LYMPHOBLASTOID CELLS AND ITS COMPARISON WITH THE EFFECT OF RETINOIC ACID.

Morigaki T, Ito Y
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Cancer Lett; 15(3):255-259 1982

Inhibitory effects of L-ascorbic acid (AA) on the induction of Epstein-Barr virus (EBV)-associated antigens in human lymphoblastoid P3HR-1 and Raji cells latently infected with EBV were studied. The effect of AA was compared with the inhibitory effect of retinoic acid (RA) in the same system; the intervening activity of AA was weaker but its cytotoxicity was re-

markably lower than that of RA. The effect of AA in varying concentrations (0.1-1,000 uM) on the induction of EBV early antigen and viral capsid antigen in the producer P3HR-1 cell system by single use of 5-iododeoxyuridine, n-butyrate, or 12-O-tetradecanoyl-phorbol-13-acetate is illustrated. (10 Refs)

63. REGULATION OF THE CELLULAR P53 TUMOR ANTIGEN IN TERATOCARCINOMA CELLS AND THEIR DIFFERENTIATED PROGENY.

Oren M, Reich NC, Levine AJ
Dept. Microbiology, Sch. Medicine, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Mol Cell Biol; 2(4):443-449 1982

The regulation of a 53,000-mol wt cellular tumor antigen, p53, in F9 embryonal carcinoma cells was investigated. Treatment of F9 cells with retinoic acid and dibutyryl ADP causes the cells to differentiate, predominantly into endoderm-like cells, and results in a marked decrease in the levels of p53. The mechanism(s) responsible for the decline in p53 in differentiated cells involves a marked decrease in the amount of in vitro translatable p53 messenger RNA. This mechanism is discussed with respect to that operating in simian virus 40 infection or transformation and which involves increased stability of the p53 protein. (22 Refs)

OTHER RELATED STUDIES

64. CHARACTERIZATION OF SOME ANTIGENS ASSOCIATED WITH THE MEMBRANE OF HAMSTER TUMOR CELLS.

Duthu A, Alexandrov I, Haddada H, Le Goffic N, Zuinghedau J, De Vaux Saint Cyr C
Institut de Recherches Scientifiques sur le Cancer (B.P. n), 8-94800 Villejuif, France
Protides Biol Fluid Proc Colloq; 29:159-162 1982

An in vitro antigen dosage was determined which characterized antigens present at the surface of nine syngeneic and non-syngeneic lines of hamster tumor cells. The results were correlated with the findings observed with the in vivo action of immunized lymphocytes in the Winn neutralization test. The cells were tested against a panel of antisera obtained from tumor-bearing hamsters or from hamsters immunized against the different cell lines maintained in cell culture. Antibody fixation on the surface of the living cells was determined by the amount of 125I-labeled staphylococcal protein A fixed on the cells. With use of the modified Winn test, splenic lymphocytes from immunized or normal hamsters together with tumor cells were injected sc in a 100:1 ratio of lymphocytes:tumor cells into naive recipients. The specific antibody fixation was demonstrated by the difference in slopes of the fixation curves between antisera and controls. Results showed that besides virus-induced antigens, the Forssman-like antigen appeared to be the most common. In the Winn neutralization test, a strong protection was observed when homologous immune lymphocytes were used while a weak cross reaction was observed with other cells. Only a small percentage of animals were protected against the graft of heterologous cells, indicating the presence at the cell membrane of cross-reacting determinants able to elicit a weak tumor rejection. (12 Refs)

65. STRUCTURAL HOMOLOGY OF A MACROPHAGE DIFFERENTIATION ANTIGEN AND AN ANTIGEN INVOLVED IN T-CELL-MEDIATED KILLING.

Kurzinger K, Ho MK, Springer T
Lab. Membrane Immunochemistry, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115
Nature; 296(5858):668-670 1982

The cellular distribution and molecular structure of two murine cell-surface antigens, macrophage differentiation antigen 1 (Mac-1) and lymphocyte function-associated antigen 1 (LFA-1) were investigated. Mac-1 is expressed on macrophages, natural killer cells and 50% of bone marrow cells, but not on B or T lymphocytes. LFA-1 is expressed on B and T lymphocytes and 75% of bone marrow cells, but not on macrophages. Mac-1 and LFA-1, which share some common antigenic determinants recognized by monoclonal antibodies, comprise a novel family of leukocyte differentiation antigens. The two antigens have alpha-chains of mol wt 170,000 and 180,000, respectively; both have beta-chains of mol wt 95,000. Cross-linking studies indicate a non-covalent association of the subunits into an alpha-1-beta-1 quaternary structure. (11 Refs)

66. A RAT MONOCLONAL ANTIBODY AGAINST MOUSE ALPHA AND BETA INTERFERON OF ALL MOLECULAR WEIGHT SPECIES.

Mannel D, De Maeyer E, Kemler r, Cachard A, De Maeyer-Guignard J
Inst. Curie, Centre Universitaire, 91405 Orsay Cedex, France
Nature; 296(5858):664-665 1982

A LOU strain rat was immunized with interferon (IFN) purified from cultures of Swiss mouse C-243 cells which had been infected with Newcastle disease virus. Spleen and mesenteric lymph node cells from the immunized rat were fused with LOU-derived 210RCY3-Agl.2.3 rat myeloma cells. The resulting hybridoma secreted monoclonal antibody of the IgG class, with binding activity to all the different mol wt species, as demonstrated by an enzyme-linked immunosorbent assay and by affinity chromatography of a crude INF preparation on columns containing bound anti-IFN antibodies. The antiviral activity of all the mol wt species was neutralized by the antibody but the neutralizing activity was much weaker than the binding activity, indicating the presence of a common antigenic site for all mouse alpha and beta IFN species. (18 Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. THE EVOLUTION, IMPLICATIONS, AND APPLICATIONS OF THE HEPATITIS B VACCINE.

Alter HJ
NIH, Bethesda, MD
JAMA; 247(16):2272-2275 1982

One aspect of hepatitis B vaccine is that it might serve indirectly as the first cancer vaccine because of the possible relationship between hepatitis B virus (HBV) infection and primary hepatocellular carcinoma (HCC). Evidence for causality is summarized. The global distribution of hepatitis B surface

HE 20.3123/2:

antigen (HBsAg) carriers and HCC are almost identical. (14 Refs)

2. PATHOBIOLOGY OF HEPATITIS B VIRUS.

Gerber MA, Thung SN
Dept. Pathology, Mount Sinai Hosp. and Sch. Medicine, City Univ. New York, New York, NY, 10029
Pathobiol Annu; 11:197-228 1981

Knowledge of the pathology of hepatitis B virus (HBV) and more recent findings are discussed. The amount of virus specified unique gene products may be limited, although combined mol wt of all polypeptides from hepatitis B surface antigens (HBsAg), hepatitis B core antigen, and a cryptic form of hepatitis B antigen (HBeAg) appear to exceed the coding capacity of the small HBV genome, which is approx 100,000 daltons of protein. Recent studies indicate that HBsAg and albumin receptor activity emerge simultaneously in hepatocellular cytoplasm of HBV infected patients and also in the cytoplasm, on the cell surface, and in the supernatant culture media of an HBsAg producing hepatocellular carcinoma (HCC) cell line. The 28 nanometer core particles of HBV can be isolated from circulating Dane particles (DP) by detergent treatment or from hepatocellular nuclei of infected liver. Observation of two populations of DP may be of great biological importance since only full particles with complete genome may be infectious, whereas empty particles may be defective and interfere with replication of homologous virus. HBeAg probably is an integral structural component of the HBV nucleocapsid, coded by the genome of the virus. In serum of HBV infected patients, HBeAg occurs free or in association with IgG, most likely as immune complexes. Diseases associated with HBV infection are acute and chronic hepatitis, and a variety of clinical syndromes may be associated with HBV infection. HBV may be one of the agents involved in the etiology of human HCC. HCC in man is highly correlated with prevalence of HBsAg carriers. Serologic markers of HBV infection are found in significantly higher frequency in patients with HCC, and tumor markers are detected in HCC cells. The possibility cannot be excluded that the virus plays a merely passive role in hepatocarcinogenesis. (228 Refs)

3. POST-TRANSFUSION HEPATITIS IN LEUKEMIA PATIENTS.

Golosova TV, Pobedinskaia IN, Liubimova LS, Beliaeva NE, Troitskaia IS
Lab. Bacteriology and Post-Transfusion Hepatitis Prevention, Central Inst. Hematology and Blood Transfusion, Moscow, USSR
Probl Gematol Pereliv Krovi; 27(3):18-22 1982

To determine the risk of hepatitis B development in leukemia patients, the incidence of hepatitis B surface antigen (HBSAG), anti-HBSAG, and antibodies against hepatitis B core antigen (anti-HBCAG) was studied in 122 patients (19-58 yr old). Among these patients, 30 had acute lymphoblastic leukemia (ALL), 20 had acute myeloblastic leukemia (AML), 31 had chronic lymphocytic leukemia (CLL), and 41 had chronic myelocytic leukemia (CML). Radioimmunoassay showed that the HBSAG incidence in leukemia patients (43,0%) was greater than 11x greater than that in healthy controls. The incidence of anti-HBSAG and anti-HBCAG in the patients with ALL and CLL was greater than that in the patients with AML and CML. (23 Refs) (In RUS)

4. SOLID TUMORS OF HUMAN PRIMARY HEPATOCELLULAR CARCINOMA CELL-LINES IN HYPOTHYMIC MICE: A MODEL FOR BIOCHEMICAL AND THERAPEUTIC STUDIES.

Hahn EG, Gauss-Muller V, Hornberger M, Kalbfleich H, Deinhardt F
Medizinische Klinik und Poliklinik, Universitatsklinikum Steglitz, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Z Gastroenterol; 20(3):168-173 1982

The behavior of human primary hepatocellular carcinoma (HPHC) cell lines was studied in nude mice. Hypothymic mice of strains Balb/c nu/nu and C57Bl nu/nu were injected sc with 1-8 x 10(7) cells from HPHC lines PLC/PRF/5, Hep3B, or Mahlavu. The first two strains produce hepatitis B surface antigen (HBsAg); Mahlavu cells do not. All three cell lines produced solid tumors that were successfully transplanted sc into additional mice. Significant differences in growth were not noted between cell line. Tumor growth was detectable within 14 days. Retransplantation allowed production of large homogeneous experimental groups and larger tumor masses. No evidence of metastasis was found in lung, liver, or spleen tissue of host animals. Tumors were separated from host tissue by capsules of connective tissue. HBsAg, alpha-fetoprotein (AFP), fibrinogen, and alpha-antitrypsin (AAT) were detected by immunofluorescence techniques in cells of PLC/PRF/5 and Hep3B tumor transplants. No positive reactions for hepatitis A or Bc virus antigens were noted. No HBsAg, AFP, fibrinogen, AAT, or hepatitis virus antigens was detected in Mahlavu tumor transplants. Growth of cells exhibiting many of the properties of the original tumors without immunosuppressive treatment of the host animals makes the nude mouse-HPHC model suitable for study of human hepatocellular carcinoma. (6 Refs) (In GER)

5. CARRIER STATUS IN HEPATITIS B: A MODERN SCOURGE WITH HOPE.

Iber FL
Univ. Maryland Hosp., Batimore, MD
JAMA; 247(16):2275-2276 1982

The importance of 'carriers' of hepatitis B is discussed. The prevalence of hepatitis B surface antigen (HBsAg) carriers in the general population of the United States is estimated to be 0.2-0.5%. The majority of these patients are entirely asymptomatic, yet the carrier at times represents a clear health hazard to his contacts. The HBsAg carrier is at clear risk of liver disease and hepatocellular carcinoma (HCC). Approx 15-20% of asymptomatic carriers have significant chronic liver disease. At least one half of all patients in whom HCC develops have associated markers of hepatitis B virus. (2 Refs)

6. CURRENT STATUS OF CLINICAL INVESTIGATION ON HEPATITIS, LIVER CIRRHOSIS AND HEPATIC CARCINOMA IN CHINA.

Lin Z
Zhongshan Hosp., Shanghai First Medical Coll., Shanghai, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(2):79-81 1981

Recent progress in the etiology, diagnostic techniques and treatments is reviewed for hepatitis, liver cirrhosis and liver cancer. The roles of hepatitis B virus, hepatitis B surface antigen, alpha-fetoproteins and numerous enzymes useful in diagnosis are specially discussed. Other topics covered include new diagnostic instrumentation, such as B-mode ultrasonography,

scintigraphy, computed tomography and fiber optics. (no Refs) (In CHI)

7. A COMPARISON OF 5'-NUCLEOTIDE PHOSPHODIESTERASE ISOENZYME AND OTHER ENZYMES IN PRIMARY HEPATIC CARCINOMA.

Lu H, Chen Q, Liu C, Yang B, Hu H, Jiang K, Ding C, Xu W
Affiliated Xinhua Hosp., Shanghai Second Medical Coll., Shanghai, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(2):82-85 1981

Although the determination of alpha-fetoprotein (AFP) has now been successfully used in the diagnosis of primary liver cancer, the false negative diagnostic rate with this technique is still about 10%. This study was undertaken in order to improve the diagnostic accuracy of liver cancer. Serum concentrations of 5'-nucleotide phosphodiesterase isoenzyme (NPI) and other commonly used enzymes (gamma-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, etc) were determined in 100 cases of primary liver cancer, 17 cases of resected primary cancer, 11 cases of metastatic liver cancer, 24 cases of liver cirrhosis and 20 cases of hepatitis positive for hepatitis B surface antigen (HBSAG). A comparison of the results showed that NPI was highly specific for liver cancer while the other enzymes were not. However, it had no significant relationship with HBSAG or serum alanine aminotransferase activities. In AFP-negative or weakly AFP-positive patients with primary liver cancer, the NPI-positive rate was high. It was concluded that NPI can complement AFP in improving primary liver cancer diagnosis. (12 Refs) (In CHI)

8. PRESENCE OF HEPATITIS B SURFACE ANTIGEN BEFORE PRIMARY HEPATOCELLULAR CARCINOMA.

Nomura A, Stemmermann GN, Wasnich RD
Japan-Hawaii Cancer Study, Kuakini Medical Center, 347 N Kuakini St., Honolulu, HI, 96817
JAMA; 247(16):2247-2249 1982

In a study of 7,498 men of Japanese ancestry in Hawaii, 18 incident cases of primary hepatocellular carcinoma were identified after a follow-up period of 13 yr. Sixteen of the 18 patients had stored serum specimens available for analysis. Ten of the 16 had positive serum test results for hepatitis B surface antigen in their original specimens. None of 48 matched control subjects, whose stored serum specimens were also analyzed, had similar positive test results. This finding indicates that hepatitis B surface antigenemia preceded primary hepatocellular carcinoma in many patients. (Author abstract) (20 Refs)

9. HEPATITIS B VIRUS AND PRIMARY LIVER CANCER: DEMONSTRATION OF A CYTOPLASMIC TUMOR ANTIGEN IN THE TRANSFORMED HEPATOCYTE.

Romet-Lemonne JL, Barin F, Goudeau A, Maupas P
Institut de Virologie de Tours, Facultes de Medecine et de Pharmacie, 2bis, boulevard Tonnelle, 37000 Tours, France
C R Acad Sci [III] (Paris); 294(1):9-14 1982

The presence of tumor antigen was studied in human hepatoma cell line PLC/PRF/5 by indirect immunofluorescence and immunoperoxidase assay using antisera from 14 Senegalese patients with primary hepatocellular carcinomas. Ten of the 14 sera were HBs Ag-positive, 4/10 also HBe Ag-positive, 3/14 anti-HBsd antibody-positive and 1/14 anti-HBc antibody-positive. Twenty-two sera without hepatitis B virus markers from African Blood donors and from cancer patients were used as controls. Tumor antigen (HBV/T) was found in the cytoplasm of the human hepatoma cells. The same antigen was also detected in primary hepatocellular carcinoma tissues. The data obtained with serum and tissue controls indicate that the HBV/T Ag-anti-HBV/T system seems to be associated with the transformation of hepatocytes by hepatitis B virus. (15 Refs) (In FRE)

10. INCREASED FREQUENCY OF HLA-DR5 IN MYCOSIS FUNGOIDES AND KAPOSI'S SARCOMA (MEETING ABSTRACT)

Safai B, Pollack MS, Myskowski L, Dupont B
Sloan-Kettering Institute for Cancer Research, New York, NY, 10021
Fed Proc; 41(3):414 1982

Mycosis Fungoides (MF) is a cutaneous T-cell lymphoma while Kaposi's Sarcoma (KS) is a multicentric neoplasm which often has its primary manifestation in the skin. Although the exact mechanism for initiation of either disease is still unknown, a viral mechanism has been suggested in both cases. Specifically, retroviruses have been associated with some tumor cell lines of MF, and cytomegaloviruses have been associated with KS. In order to investigate the possible role of HLA-associated variations in genetic susceptibility, 64 patients with histologically documented MF and 32 patients with histologically documented KS were typed for HLA-A,B,C antigens. Most of these patients were also typed for HLA-DR antigens. A significant increase in DR5 was the only statistically significant deviation in HLA antigen frequencies in either group (50% in MF and 60% in KS in comparison with 20% in controls). The increase in DR5 was especially striking in the subgroup of KS patients with the particularly aggressive form of KS recently described in young homosexual males. HLA-DR5 has also been associated with scleroderma and juvenile rheumatoid arthritis. Immunologic alterations are involved in the pathogenesis of both, but viral infection may also be a factor. The associations of MF and KS with DR5 thus suggest that some individuals with the DR5 antigen may be at higher genetic risk for virally initiated neoplastic diseases, possibly through an HLA-linked effect in the immune system. (no Refs)

11. CLINICAL AND LABORATORY FEATURES OF KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN (MEETING ABSTRACT)

Kris M, Safai B, Myskowski P, Koziner B, Urmacher C, Gold J, Armstrong D, Pinsky C, Krown S, Ochoa M, Sherlock P
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Soc Clin Oncol; 1:C-700 1982

A cluster of Kaposi's Sarcoma (KS) cases has been observed among young homosexual men in the New York City area. Ten patients (pts), all with the onset of symptoms after 12/78, have been seen. THe median age was 38 years (range 32-55); 9 were white and 1 was an American black. Initial sites of disease were skin (8) and oral mucosa (2). Lymphadenopathy was seen in 7 pts and hepatosplenomegaly in 1 on initial examination. One pt had Pneumocystis carinii pneumonia at diagnosis. Gastrointestinal involvement was documented in 5 of 7 pts completely evaluated by either endoscopy or necropsy. Cytomegalovirus (CMV) titers were greater than 1:32 in 9 pts; 1 was anticomplementary. One pt had a 4-fold rise in CMV titer during his illness. Epstein-Barr viral capsid antigen titers, measured by the immunofluorescent antibody technique, were greater than 1:160 in 9 pts tested. CMV was cultured from the urine of 2 of 7 pts. Oral cultures grew Candida albicans in 3 pts. Antibody to hepatitis B was noted in all 5 tested pts. Serum immunoglobulins G, A, and M were normal or elevated in all 6 pts tested. Significantly lower ratios of T-helper

(OKT4+) to T-suppressor (OKT8+) cells were noted in KS pts when compared to normal controls using anti-T-cell monoclonal antibodies. Two of the 10 pts died 10 and 16 months after histologic diagnosis despite treatment with chemotherapy. No other pts have received chemotherapy to date. (no Refs)

12. A RETROVIRUS ASSOCIATED WITH HUMAN ADULT T CELL LEUKEMIA: IN VITRO ACTIVATION.

Hinuma Y, Gotoh Y, Sugamura K, Nagata K, Goto T, Nakai M, Kamada N, Matsumoto T, Kinoshita K
Inst. Viral Res., Kyoto Univ., Shogoin Kawahara-machi, Sakyo-ku, Kyoto 606, Japan
Gan; 73(2):341-344 1982

Presence of adult T cell leukemia antigen (ATLA) was studied in the mononuclear cell fractions of peripheral blood derived from 11 patients (9 men, 2 women; 48-83 yr old) with adult T cell leukemia (ATL), from a 54-yr-old man with mycosis fungoides (MF), and from 8 healthy adults (6 men, 2 women; 21-44 yr old). The mononuclear cell fractions were cultured in the presence and/or absence of interleukin-2 (IL-2) or T cell growth factor. Some of the fractions were also examined with electron microscopy for virus particles. ATLA positive cells were not detected in any of the cell preparations examined prior to culturing. However, ATLA-bearing cells were observed in the cultures from 6/11 ATL patients and 1/2 ATLA antibody-positive healthy subjects. No ATLA-bearing cells were detected in cultures of one patient with MF and six ATLA antibody-negative healthy subjects. High percentages of ATLA positive cells were found 2-3 days after starting cultures without IL-2; the ATLA were located in the cytoplasm of rather small leukemic cells and were often aggregated. The ATLA-bearing cells in cultures supplemented with IL-2 for a greater than 2 wk were large and often multinuclear with blastoid morphology. Presence of Type C virus particles was observed with electron microscopy in ATL-derived cultures with a high percentage of ATLA positive cells. The results showed that (1) peripheral blood cells of many patients with ATL contain sufficient information for ATLA or ATL virus (ATLV) formation in a repressed form, and suggest that (2) ATLA is associated with ATLV and (3) ATLV is present not only in ATL patients but also in anti-ATLA positive healthy individuals. (6 Refs)

13. ESTABLISHMENT AND CHARACTERIZATION OF A HUMAN MYELOMA CELL LINE (KMM-1).

Togawa A, Inoue N, Miyamoto K, Hyodo H, Namba M
Dept. Internal Medicine, Kawasaki Medical Sch., Kurashiki-shi, Japan
Int J Cancer; 29(5):495-500 1982

A new cell line (KMM-1) was established from a subcutaneous plasmacytoma of a 62-yr-old male with multiple myeloma. Immunological studies indicated that cultured cells were derived from the same clone of myeloma cells in vivo: smeared cells were stained with fluorescein-conjugated globulin of antisera monospecific to lambda-chain, and lambda-chains in the cell extracts and in culture media were identical to the Bence-Jones protein found in the patient's urine. The cell line grew in suspension with a doubling time of 36-40 hr and contained primitive plasmablastoid cells with prominent nucleoli and rough endoplasmic reticulum. Cells had the karyotype of 47, X, -Y, Iq+,-2, +t(1:2) (cen:cen), +7, 12q+, 14q+, +mar and carried no Epstein-Barr virus-determined nuclear antigen. Surface markers were as follows; E rosette (-), IgG Fc receptor (-), C3 receptor (-), S-Ig (+), TdT (-), asialo-GM1 (-). The reasons for the successful establishment of the myeloma cell line are discussed. (Author abstract) (23 Refs)

14. A HETEROANTISERUM AGAINST AMERICAN BURKITT'S LYMPHOMA (BL) (MEETING ABSTRACT)

Magrath IT, Parsons RG
Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:1039 1982

We have raised a goat antiserum (B75) against purified membrane from an American BL cell line and examined its spectrum of reactivity after extensive absorption with either 5 African BL cell lines or 6 Epstein Barr Virus-transformed cord blood lymphocyte (CBL) cell lines. Both methods of absorption yielded antisera with identical specificities. Eleven of 12 EBV genome-negative cell lines derived from American BL (6) and undifferentiated non-BL (6) reacted with B75 using indirect immunofluorescence. Three of 4 EBV genome-positive American undifferentiated lymphomas were also positive, but none of 13 CBL lines or 8 non-tumor lymphoblastoid cell lines reacted with B75. Two of 7 African BL cell lines reacted positively. These 2 lines also secreted small amounts of IgM, whereas none of the 5 negative lines did so. B75 did react with blast cells derived from common acute lymphoblastic leukemia (ALL) but not with blast cells from T-cell ALL or lymphoblastic lymphoma. B75 reactivity persists after incubation of cells with proteolytic enzymes and we have so far been unable to immunoprecipitate a protein from cell lysates with B75. These data indicate that BL cells express one or more antigens not present on other lymphoid cell lines of normal and neoplastic origin. These data are consistent with the hypothesis that American-BL and undifferentiated lymphoma are the neoplastic counterparts of cell types early in the B-cell pathway, probably immediately after the pre-B cell stage, and before the normal counterpart of African BL. (no Refs)

15. DETECTION AND QUANTITATION OF IMMUNOGLOBULINS ASSOCIATED WITH TUMORS OF THE HUMAN ORAL CAVITY.

Pillai S, Sasidharan VK, Balaram P, Vivekanandan S, Vasudevan DM
Regional Cancer Center, Medical Coll. Campus, Trivandrum 695 011, India
Indian J Cancer; 19(1):44-46 1982

IgA and IgM were quantitated by radial immunodiffusion on agar plates containing IgA, IgG and IgM antisera. Alpha amylase activity was measured in tissue extracts to eliminate saliva contamination which contains high amounts of IgA. IgA and IgG were found only in tumor extracts, supporting the concept of tumor associated antibodies. Potassium chloride was used to extract membrane integral proteins or membrane bound proteins and no IgG was quantitated in these extracts. This suggests that IgG may be present in the cytoplasmic portion of the cell extract or present on the surface of tumor cells attached to other membrane proteins. The role of herpes simplex virus in pathogenesis of oral cancer is discussed; cells transformed by DNA viruses carry virus specific antigens. Immunoglobulins in tumor extracts might also be a reaction to these virus specific antigens. (19 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

16. A STUDY OF HLA AND DRW ANTIGENS IN SEVERE RECURRENT HERPES PROGENITALIS (HSV-2) INFECTION.

Ahmed AR, Strom H, Bierman S, Myers-Elliot R, Tiwari P, Terasaki PI
Div. Dermatology, UCLA Sch. Medicine, CHS 52-121, Los Angeles, CA, 90024
J Am Acad Dermatol; 6(5):898-901 1982

HLA-A, HLA-B, HLA-C, and HLA-DR antigen distribution was studied in 93 white men (20-53 yr old, mean age 34 yr) with recurrent herpes progenitalis (RHP) to determine whether specific genetic and immunologic factors regulate the expressivity and predilection to RHP infection. Data are expressed as phenotypic frequency in 558 controls compared with simultaneously typed patients with RHP. The only antigens showing significant frequencies were HLA-A2, HLA-A3, HLA-Bw22, and HLA-Bw51. If probabilities were corrected for the number of antigens tested (39), no antigens showed a significant frequency of less than or equal to 0.05. The results of typing for HLA-DR antigens in 87 patients and 281 controls are presented. The frequency of DRw7 increased significantly in the patient group (p less than or equal to 0.009). This increase was also significant when the p value was multiplied by 6, the number of DR antigens studied in the sample. The relative risk associated with the antigens was 2.1. No statistically increased frequency of HLA-B5 or DRw5 was observed. No increased incidence of HLA-Aw31 or HLA-A1 was observed. Results added significant information to the interaction between the host and the virus that is determined by genetic predisposition. The limitations of the study are that only white men in the Los Angeles area were studied. (25 Refs)

17. EXPERIMENTAL TRANSPLACENTAL INFECTION OF PREGNANT DOGS WITH CANINE HERPESVIRUS.

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Am J Vet Res; 43(5):844-850 1982

Fetal infection was established in 28 of 33 pups obtained from seven pregnant dogs (47th to 53rd day of gestation) inoculated iv with canine herpesvirus (CHV). The pathogenesis of transplacental CHV infection was investigated by using pathologic examination, immunofluorescence microscopy, and viral assay. Infection with the virus was recognized in 13 of 18 neonatal pups obtained from four bitches by spontaneous delivery at full term. Eleven pups died with a wk of birth and all had characteristic lesions of CHV infection. Thirteen live-born and 2 stillborn pups derived from three bitches by cesarean section died within 9 days of birth. Characteristic lesions of CHV infection were observed in various organs, such as liver, spleen, kidney, and lung. Fourteen of the fetal placentas had variable degree of necrotizing lesions. The lesions were characterized by degenerative changes and focal necrosis in the placental labyrinth. Lesions were present in the walls of allantoic blood vessels. Intranuclear inclusions were evident in degenerating trophoblast cells and in the cells of maternal and fetal blood vessels. Infective virus and viral antigen were detected in the various organs of pups and in the trophoblastic cells of junctional zone. Virus also was found in the walls of maternal and fetal blood vessels of the placental tissues. The results strongly indicated that transplacental transmission of CHV may occur in pregnant dogs at a late stage of gestation. (Author abstract) (20 Refs)

18. EPSTEIN-BARR VIRUS-LYMPHOID CELL INTERACTIONS. III. EFFECT OF CONCANAVALIN A AND SACCHARIDES ON EPSTEIN-BARR VIRUS PENETRATION.

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J Virol; 42(2):402-410 1982

To study some aspects of Epstein-Barr virus (EBV) penetration into target cells, the effect of concanavalin A (ConA) and various saccharides on virus infectivity and cell susceptibility to EBV infection was examined. ConA treatment of the target cells, EBV, or EBV-cell complexes was found to inhibit virus antigen expression. Several control experiments with alpha-D-methyl-mannoside elution of ConA, removal of nonfused EBV particles from the cell surface by trypsin treatment, and addition of ConA at different times postinfection were performed to define the site of ConA action on EBV infection. ConA appeared to have a dual action: (i) it inhibited EBV binding to virus receptors, and (ii) it blocked the penetration of receptor-bound virus into target cells at a trypsin-sensitive stage, thus indicating that ConA prevented the fusion of viral envelope with the target cell membrane. A high sucrose concentration (0.25 M), known to inhibit cell membrane movements, was also found to block EBV penetration at a trypsin-sensitive stage, thus suggesting the implication of cell membrane movements and underlying activities (or both) in viral envelope fusion. Lower concentrations of various monosaccharides (0.12 M) did not influence EBV infection. Under conditions of ConA treatment that did not influence EBV infectivity and target cells susceptibility, ConA was able to mediate virus binding to EBV receptor-negative cell lines, but no virus antigens were expressed in these cells. These observations reinforced the idea that the mere attachment of EBV to lymphoid cells is not sufficient to lead to infection. In light of the present and previously published data, we postulate the existence of a specific cellular mechanism that allows the penetration of EBV into the target (B) lymphocyte. (Author abstract) (37 Refs)

19. EPSTEIN-BARR VIRUS (EBV) GENOME IN HUMAN LYMPHOMA CELLS AMPLIFIES EXPRESSION OF THE PROVIRAL MURINE LEUKEMIA VIRUS (MULV) P30 (MEETING ABSTRACT)

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Fed Proc; 41(3):1387 1982

EBV-negative lymphoma lines, Ramos and BJAB, can be converted in vitro to EBV-positive sublines thus providing a uniclonal tumor cell population in which the same line can be compared with and without the EBV genome. We have used this system to distinguish between trivial subline difference and differences related to the presence of the EBV genome. The antigenic profiles of plasma membranes were examined using sera from immunized rabbits. Tumor cells proteins were resolved by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and then electrophoretically transferred to nitrocellulose paper. Anti-tumor cell sera was allowed to bind to the antigens. Binding was detected using 125I-labeled antibodies to the IgG of the primary sera, followed by autoradiography. Electro-blotting revealed several distinct differences. A major difference was an increase in a 30K dalton protein (p30) in the Ramos converted sublines. In contrast, no p30 seen in BJAB or its converted lines. When Ramos, but not BJAB, was originally established in culture, it was passaged in athy-

mic nude mice and acquired an MuLV provirus. Present results suggested that the EBV-genome in Ramos converted cells amplified expression of the mouse p30. This conclusion was confirmed using antisera specific for MuLV and p30. How EBV is promoting enhancement of retroviral proteins in these human lymphoma cells and its possible biological significance is not clear. (no Refs)

20. MEMBRANE ANTIGEN ON EPSTEIN-BARR VIRUS-INFECTED HUMAN B CELLS RECOGNIZED BY A MONOCLONAL ANTIBODY.

Slovin SF, Frisman DM, Tsoukas CD, Royston I, Baird SM, Wormsley SB, Carson DA, Vaughan JH
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Proc Natl Acad Sci USA; 79(8,part1):2649-2653 1982

This paper describes a monoclonal antibody (B532) that detects a membrane antigen present on greater than or equal to 95% of the B cells from lines carrying the Epstein-Barr virus (EBV) genome. Evidence suggesting that B532 is EBV-related was originally obtained by using a cell-binding radioassay with different cell line substrates. Immunofluorescence and cell-sorter analysis confirmed that the antigen was present in high density on all EBV-infected lymphoblastoid B-cell lines, but not on EBV-negative B-, T-, myeloid, or null cell lines. Isolated normal peripheral blood B and T lymphocytes and monocytes failed to bind B532. The monoclonal antibody did not inhibit in vitro EBV infection nor did it block the killing of EBV-infected targets by cytotoxic T lymphocytes. The cell surface antigen recognized by B532 was shown by immunoprecipitation to have a mol wt of approx 45,000. (Author abstract) (38 Refs)

21. A MURINE MODEL SYSTEM FOR STUDYING THE MOLECULAR MECHANISM OF EPSTEIN-BARR VIRUS (EBV)-MEDIATED CELL TRANSFORMATION AND CARCINOGENESIS (MEETING ABSTRACT)

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Fed Proc; 41(3):688 1982

EBV can normally infect in vitro only human and marmoset B lymphocytes, leading to cell transformation without any primary viral reproductive cycle. Using our method of EBV receptor-implantation we demonstrated that any other cell which is artificially provided with EBV receptors can be infected by the virus. Here we show also that EBV receptor-implanted mouse lymphocytes are infectible by EBV, when using either the transforming B-95-8 (B-EBV) or non-transforming P3HR-1 (P-EBV) substrains of the virus. Unlike the natural host, mouse lymphocytes are not readily transformed by B-EBV. Instead, the cells support a full viral lytic cycle, resulting in the release of a new biologically active EBV isolate (M-EBV). Unlike the natural host, the EBV-infected mouse cells express the virus-determined early (EA) and virus capsid (VCA) antigens. Suprisingly, the EBV-nuclear antigen (EBNA) is barely detectable. This model system is used to test the hypothesis that the EBV-related oncogenic mechanism involves a virus-mediated increase in intracellular proteins, presumably as a complex between a virus coded 48,000 dalton component and a cell-coded 53,000 dalton component, which may block the viral lytic cycle and interfere with cell differentiation leading to transformation. (no Refs)

22. CELLULAR PROTEINS REACTIVE WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST SIMIAN VIRUS 40 T-ANTIGEN.

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J Virol; 42(2):612-620 1982

Several recently isolated monoclonal antibodies which reacted with simian virus 40 T antigens also reacted with proteins found in uninfected and untransformed cells. The proteins were different from each other, PAb419 reacting with a 35,000-mol-wt protein, PAb427 reacting with a 75,000-mol wt phosphoprotein, PAb405 reacting with a 150,000-mol-wt phosphoprotein, and PAb204 reacting with a 68,000-mol wt protein. It is suggested that although some of these cross-reactions may be fortuitous, they may, as an alternative, reflect similarities of shape and perhaps function between domains of the viral T antigen and the relevant host proteins. (Author abstract) (29 Refs)

23. DIFFERENT FORMS OF SIMIAN VIRUS 40 LARGE TUMOR ANTIGEN VARYING IN THEIR AFFINITIES FOR DNA.

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J Virol; 42(2):456-466 1982

In various permissive monkey cell lines infected with simian virus 40 there are two major forms of large T antigen which differ in their rate of sedimentation through sucrose gradients. The lighter (5 to 7S) form sedimented slightly more rapidly than the 4S tRNA marker, whereas the heavier (16S) form sedimented slightly more slowly than the 18S rRNA marker. The small t antigen did not form complexes which sedimented as rapidly as those formed by the large T antigen. The 16S T antigen form was converted to the slowly sedimenting 5 to 7S form in the presence of 1.0 M NaCl. The majority of large T antigen synthesized in cell-free protein-synthesizing systems primed by mRNA isolated from infected cells sedimented as the 5 to 7S form even when premixed with excess quantities of cellular T antigen. The formation of the 16S form in infected cells did not require ongoing viral or cellular DNA replication because considerable quantities of this T antigen class were produced in the presence of DNA synthesis inhibitors, such as cytosine cytosine arabinoside. Both 5 to 7S and 16S forms could be isolated separately and, therefore, each could be analyzed as to its individual properties. The 5 to 7S T antigen form bound more efficiently and tightly to DNA and had specific affinity for sequences at the viral origin of replication, whereas the 16S form bound less efficiently to DNA and exhibited very little specificity for origin-containing DNA sequences. It is therefore likely that the active DNA-binding species of T antigen isolated from infected cells is the 5 to 7S form. (Author abstract) (43 Refs)

24. GENETIC ANALYSIS OF TUMORIGENESIS. VIII. SUPPRESSION OF SV40 TRANSFORMATION IN CELL HYBRIDS AND CYTOPLASMIC TRANSFERANTS.

Howell N, Sager R
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Cytogenet Cell Genet; 31(4):214-227 1981

Intraspecies somatic cell hybrids of BALB/c mouse 3T3 and SV40-transformed embryonic fibroblast (SVT2) cells were ana-

lyzed for transformation-associated properties and their tumorigenic potential in nude mice. In confirmation of our earlier findings, hybrids expressing the viral T-antigen were not suppressed for the ability to clone in medium with 1% serum. In contrast, division rate in medium with 1% and 10% serum, anchorage independence, cytochalasin-sensitive growth control, and tumorigenicity were suppressed noncoordinately, and the extent of suppression varied from one hybrid to another. Suppression was not simply determined by the increased chromosome content of the hybrid cells, nor was suppression correlated with rearrangements of the integrated viral sequence. Similar results were found in cytoplasmic transferants expressing T-antigen. Four independent transferants and subclones derived from them varied in the extent of suppression of anchorage independence and tumorigenicity. In both hybrids and transferents, a low serum requirement for clonal growth apparently was determined solely by expression of SV40 T-antigen, but other transformation properties, as well as tumorigenicity, appeared to require multiple changes in the cellular genome for their expression. These changes must occur during or after viral integration, since they are not expressed in uninfected 3T3 cells. (Author abstract) (47 Refs)

25. INTRACELLULAR TRANSPORT OF SV40 LARGE TUMOR ANTIGEN: A MUTATION WHICH ABOLISHES MIGRATION TO THE NUCLEUS DOES NOT PREVENT ASSOCIATION WITH THE CELL SURFACE.

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Virology; 119(1):169-184 1982

The cT mutation of PARA, an SV40-adenovirus 7 hybrid virus, abolishes the transport of SV40 T-antigen (T-ag) to the nucleus and results in the accumulation of T-ag in the cytoplasm of infected and transformed cells. The effect of the cT mutation on the association of T-ag with the cell surface was examined in PARA(cT)-infected monkey cells. Surface-associated T-ag was detected by immunofluorescence, lactoperoxidase-catalyzed cell-surface iodination, and cellular fractionation. Surface-associated T-ag was more readily labeled by cell-surface iodination with PARA(cT)-infected cells than with SV40 and wild-type PARA [PARA(nT)]-infected cells. Control experiments eliminated the possibility that the enhanced detection of T-ag in PARA(cT)-infected cells was due to the labeling of intracellular T-ag by lactoperoxidase or to T-ag leaking from dead cells and adhering to the cell surface. The elevated level of surface-associated T-ag in PARA(cT)-infected cells was confirmed by metabolic labeling and cellular fractionation, indicating that the increased iodination of surface-associated T-ag was due to a greater number of T-ag polypeptides on the surface rather than a greater exposure of tyrosine residues. Pulse-chase experiments demonstrated that the elevated level of surface-associated T-ag in PARA(cT)-infected cells was not due to a prolonged stability of surface-associated T-ag. The cT mutation provides a useful tool for studies of mechanisms governing intracellular protein transport. (Author abstract) (47 Refs)

26. BIOLOGICAL AND BIOCHEMICAL STUDIES OF AFRICAN GREEN MONKEY LYMPHOTROPIC PAPOVAVIRUS.

Takemoto KK, Furuno A, Kato K, Yoshiike K
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J Virol; 42(2):502-509 1982

The growth of African green monkey lymphotropic papovavirus (LPV) in human lymphoblastoid cell line BJA-B was found to be slow and inefficient due to the accumulation of defective particles. An analysis of molecularly cloned LPV DNAs showed that 3 of 19 clones had DNAs that were longer (5.1 kilobases) than the DNAs of the other clones. The 5.1-kilobase DNA was infectious for BJA-B cells, whereas the shorter (4.8-kilobase) molecules were defective. Unlike the wild-type virus, stocks of LPV made from cloned, infectious DNAs were homogenous and had higher titers. Using stocks of nondefective LPV, we investigated other biological properties. LPV replication in another human B-lymphoblastoid cell line was observed. The virus did not cause tumors when it was inoculated into newborn hamsters. Serological surveys of human and nonhuman primate sera indicated that virtually all primates, including humans, show evidence of infection by viruses antigenically related to LPV. (Author abstract) (29 Refs)

27. POLYOMA VIRAL MIDDLE T-ANTIGEN IS REQUIRED FOR TRANSFORMATION.

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J Virol; 42(2):621-629 1982

To determine whether small or middle T-antigen (or both) of polyoma virus is required for transformation, we constructed mutants of recombinant plasmids which bear the viral oncogene and measured the capacity of these mutants to transform rat cells in culture. Insertion and deletion mutations in sequences encoding small and middle T-antigens (79.7, 81.3, and 82.9 map units) rendered the DNA incapable of causing transformation by the focus assay. Similar mutations in sequences that encoded middle but not small T-antigen (89.7, 92.1, and 96.5 map units) generally abolished the transforming activity of the DNA. However, two mutants (pPdl1-4 and pPdl2-7) that carried deletions of 92.1 map units retained the capacity to transform cells; pPdl1-4 did so at frequencies equal to those of the parental plasmid, whereas pPdl2-7 transformed at 10% the frequency of its antecedent. From these studies we conclude that small T-antigen alone is insufficient to cause transformation and that middle T-antigen is required for transformation, either in combination with small T-antigen or by itself. (Author abstract) (43 Refs)

28. DEPENDENCE OF TUMOR-FORMING CAPACITIES OF CELLS TRANSFORMED BY RECOMBINANTS BETWEEN ADENOVIRUS TYPES 5 AND 12 ON EXPRESSION OF EARLY REGION 1.

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J Virol; 42(2):708-718 1982

Recombinants between an adenovirus Type 5 (Ad5) deletion mutant and the Ad12 DNA fragment containing early Region 1 (E1) were isolated from cells cotransfected with the EcoRI-C fragments of Ad12DNA and Ad5 dl312 (deletion in E1A) DNA (rcA) and from cells cotransfected with the SalI-C frag-

ment of Ad12 DNA and Ad5 dl312 DNA (rcB). No recombinant was isolated from cells cotransfected with Ad5 dl313 (deletion in E1B) DNA and restriction fragments of Ad12 DNA. Both rcA and rcB are defective and able to replicate in human embryo kidney (HEK) and KB cells with complementation by dl312. Both rcA and rcB formed Ad12 T antigen g, but not T antigen f, in infected HEK and KB cells. In rcA- and rcB-infected cells, Ad5 E1B and Ad12 E1A genes are transcribed. Heteroduplex and size analysis of rcA-1 or rcB-1 DNA fragments hybridized with Ad12 DNA revealed that rcA-1 DNA has a deletion between 5 and 15 map units with an insertion of a portion of Ad12 DNA (10%) and that rcB-1 DNA has a deletion between 70 and 80 map units with an insertion of a portion of Ad12 DNA (10%). The transformed cell lines, RCAY and RCBY, were established after infection of rat 3Y1 cells with rcA and rcB, respectively. Both Ad5 and Ad12 DNA sequences are contained in these cells. In RCAY cells, Ad12 T antigen g is detected, but Ad12 T antigen f is not. In RCBY cells, both Ad12 T antigens g and f are detected. Only the Ad12 E1A gene is transcribed in RCAY cells, whereas Ad5 E1B, Ad12 E1A, and Ad12 E1B genes are transcribed in RCBY cells. In soft-agar cultures, RCBY cells form large colonies, whereas RCAY cells form only tiny colonies. RCBY cells form tumors as efficiently as 12WY cells in transplanted rats. RCAY cells formed tumors inefficiently. Ad5-transformed 5WY cells do not form tumors. These observations indicate that the efficient tumor formation by RCBY cells is dependent on the expression of the Ad12 E1A and E1B genes, whereas the inefficient tumor formation by RCAY cells is due to the expression of only the Ad12 E1A gene. (Author abstract) (28 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

29. HORMONE-DEPENDENT TERMINAL DIFFERENTIATION IN VITRO OF CHICKEN ERYTHROLEUKEMIA CELLS TRANSFORMED BY TS MUTANTS OF AVIAN ERYTHROBLASTOSIS VIRUS.

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Cell; 28(4):907-919 1982

Chicken erythroblast cell strains and a cell line transformed by ts mutants of avian erythroblastosis virus (AEV) terminally differentiate when shifted to the nonpermissive temperature (42 C). The differentiated cells resemble mature erythrocytes with respect to morphology and ultrastructure, expression of differentiation-specific cell surface antigens, pattern of protein synthesis and hemoglobin content. Terminal differentiation is dependent on conditions favoring the differentiation of normal erythroid progenitor cells, including an erythropoietin-like factor. Colonies of ts AEV cells grown at 42 C in semisolid medium resemble erythrocyte colonies derived from normal erythroid progenitor cells. The colonies obtained were comparable in size or slightly larger than the late erythroid precursor (CFU-E) colonies. These results suggest that AEV-transformed cells are blocked at a stage of differentiation that is more advanced than that of the uninfected target cells. ts AEV cells are irreversibly committed to terminal differentiation within 20 to 30 hr after shift to 42 C. (Author abstract) (42 Refs)

30. VACCINATION AGAINST BOVINE LEUKEMIA VIRUS (BLV) INFECTION (MEETING ABSTRACT)

Theilen G, Ruppanner R, Miller J
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Proc Am Assoc Cancer Res; 23:1094 1982

An attempt has been made to protect cattle against BLV infection using viable and lyophilized BL-3 lymphoid cell suspension cultures. One group of 6 month-old cattle were vaccinated once with viable BL-3 cells alone and 2X with 10% suspension of aluminum hydroxide adjuvant pH 7.2. Another group of 6 month-old cattle were vaccinated 3X with lyophilized BL-3 cells with 10% suspension of aluminum hydroxide adjuvant pH 7.2. Control and vaccinated cattle were challenged 2 weeks after the last vaccination with viable BLV using 2.5x10(5) infected lymphocytes. Results indicated a protective factor in the BL-3 cells. To test the long term effects of vaccine, young uninfected cattle were vaccinated in a commercial herd in which there is a high rate of BLV infection in adult cattle. About 6 months post vaccination cattle were challenged by contact exposure and continuously thereafter. Results of the long term nature exposure trial are pending. The protective factor is unknown although it is not BLV or a subunit protein because BL-3 cells are not BLV producers. Protective factor probably is tumor associated transplantation antigens since BL-3 cells are a continuous cell line derived from a calf with lymphoma. Test and slaughter programs have proved successful in elimination of BLV infection in some countries but it would be economically prohibitive in countries with widespread BLV infection rates, such as the USA and Canada. (no Refs)

31. BREAST CANCER SKIN TEST ANTIGENS OF INCREASED SENSITIVITY PREPARED FROM VESICULAR STOMATITIS VIRUS-INFECTED TUMOR CELLS.

Austin FC, Boone CW, Levin DL, Cavins JA, Djerassi I, Rosner D, Case R, Klein E
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Cancer; 49(10):2034-2042 1982

Crude membrane (CM) extracts were prepared from five cultured breast tumor lines (MDA-MB-157, MDA-MB-231, ZR75-1, HSO578T, and MCF-7) which had been infected with vesicular stomatitis virus (VSV) to augment their antigenicity. In skin test trials, CM extracts of uninfected MCF-7 cells elicited positive responses in 0 of 13 (0%) tests in breast cancer patients, while VSV-MCF-7 elicited positive responses in 11 of the same 13 patients (84.6%). CM extracts of VSV-ZR75-1 and VSV-MCF-7 elicited greater delayed hypersensitivity responses (mm induration at 48 hr) in breast cancer patients than in patients with lung carcinoma or melanoma. Although the sensitivity of VSV-ZR75-1 was too low (10 of 28, or 35.7%, of tests positive) to be useful as a skin test antigen, VSV-MCF-7 elicited positive responses in 30 of 38 (78.9%) tests in breast cancer patients, as compared to 2 of 15 (13.3%) and 2 of 13 (15.4%) of tests in patients with lung carcinoma and melanoma, respectively. The 'virus-augmented' CM extract of cultured MCF-7 cells exhibited markedly greater sensitivity as compared to control MCF-7 extracts (p less than .005), with a high degree of specificity for breast cancer patients as compared to patients with the other neoplasms (p less than .00001). The results of skin testing with VSV-MCF-7 CM extracts demonstrated antigenic cross-reactivity with a large number of breast cancer patients, a finding of great importance for any potential immunotherapy and/or immunodiagnosis. (Author abstract) (27 Refs)

32. IDENTIFICATION OF A FISH PROTEIN ASSOCIATED WITH A KINASE ACTIVITY AND RELATED TO THE ROUS SARCOMA VIRUS TRANSFORMING PROTEIN.

Barnekow A, Schartl M, Anders F, Bauer H
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Cancer Res; 42(6):2429-2433 1982

Cells of all vertebrates thus far investigated contain a cellular src gene, which appears to be a highly conserved homolog of the Rous sarcoma virus oncogene src. Similar to the Rous sarcoma virus oncogene src, this endogenous cellular src gene codes for a Mr 60,000 phosphoprotein (pp60c-src) which is associated with a kinase activity. This kinase specifically phosphorylates tyrosine residues of proteins. We have systematically looked for pp60c-src in specific strains of certain teleostean fish, including the genera Xiphophorus and Girardinus. These strains are known to contain chromosomal oncogenes causing neoplastic transformation in certain mutants and hybrids. Since the pp60c-src found in other species has been shown to be antigenically related to the viral src gene product, a phosphoprotein with a molecular weight of 60,000 (pp60r-src), we have used tumor-bearing rabbit serum which recognizes Rous sarcoma virus pp60src to detect such a related protein in fish. Tumor-bearing rabbit serum precipitated two proteins with molecular weights of 60,000 and 52,000. The Mr 60,000 phosphoprotein was associated with a protein kinase activity that phosphorylates tyrosine residues of the immunoprecipitating immunoglobulin G heavy chain (Mr 53,000). The antigenic relationship of this fish protein to viral pp60src was further documented by an immune competition assay. We conclude, therefore, that the fish Mr 60,000 phosphoprotein is a pp60c-src encoded for by a fish cellular src gene that corresponds to the viral src oncogene. The Mr 52,000 phosphoprotein is probably a proteolytic degradation product of pp60c-src. All animals of the various strains of the fish investigated in this study showed kinase activity that was reactive upon immunoprecipitation with tumor-bearing rabbit serum, indicating that the pp60c-src protein is a normal constituent of the fish. Measurable quantitative differences were revealed between the various strains as well as in different tissues. Whereas brain and melanoma tissue showed a high kinase activity when compared to skin, liver, spleen, and testes, muscle tissue displayed no significant activity. (Author abstract) (27 Refs)

33. IDENTIFICATION OF TUMOR-ASSOCIATED ANTIGENS ON ULTRAVIOLET LIGHT-INDUCED TUMORS USING ANTITUMOR ANTIBODIES DEVELOPED IN ASCITES FLUID.

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Cancer Res; 42(6):2371-2375 1982

A method is described which leads to the production of large amounts of ascites containing antitumor antibody in small numbers of mice. The antibody was then used to identify and characterize tumor-associated antigens on an ultraviolet light-induced murine skin fibrosarcoma. The antibody showed specific complement-dependent cytotoxicity to the homologous tumor and to an allogeneic tumor line which displayed a glycoprotein viral determinant with a mol wt of 70,000 on its surface. Absorption of the immune ascites with other tumor cell lines removed the cytotoxicity in relation to the presence of the glycoprotein. Isolation of the tumor cell surface components binding antibody revealed two components with mol wt of approx 70,000 and 60,000. The Mr 70,000 component was identified as viral gp70 by peptide mapping. (Author abstract) (27 Refs)

34. IDENTIFICATION AND CHARACTERIZATION OF TUMOR-SPECIFIC ANTIGENS USING ASCITES INDUCED IN SYNGENEIC MICE (MEETING ABSTRACT)

Frey JL, Fortner GW, Takemoto L, Consigli RA
Kansas State University, Manhattan, KS, 66506
Proc Am Assoc Cancer Res; 23:1071 1982

Ascites induced in C3H mice by IP immunizations with the UVL-induced tumor cell line 1591 in Freund's complete adjuvant was used to identify cell surface tumor associated antigens (TAA). Using immunofluorescence assay, the ascites showed binding to the homologous cell line and to a lesser degree binding to the syngeneic heterologous tumor cells. The antibody showed specific complement-dependent cytotoxicity to the homologous tumor and an allogeneic tumor line which displayed the viral determinant gp70 on its surface. Adsorption of the immune ascites with other tumor cell lines removed the cytotoxicity in relation to the presence of gp70. To look at the determinants more closely, 125I-lactoperoxidase-labelled cell surface components bound to antibody were isolated with Protein-A and electrophoresed in SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis). Autoradiography showed two bands, a major band of 70K and a minor band of 60K. Peptide mapping showed the 70K to be gp70. The 60K could be a unique TAA on 1591 cells. These experiments illustrate the need for determining the role retrovirus expression might play in the interactions of chemically and physically induced tumors with their hosts. (no Refs)

35. IMMUNOLOGIC RELATEDNESS OF INTRACISTERNAL A-PARTICLES IN MOUSE EMBRYOS AND NEOPLASTIC CELL LINES.

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JNCI; 68(4):643-649 1982

Murine intracisternal A-particles (IAP) are retroviruses expressed in large numbers in certain neoplastic cells and preimplantation mouse embryos. Immuno-electron microscopic detection of IAP-associated antigens in mouse rhabdomyosarcoma cells and early mouse embryos provides the first direct evidence that IAP produced by these two sources are serologically related. In both embryos and cells, data suggest that, after synthesis, IAP core protein rapidly associates with the endoplasmic reticulum. In addition, in embryos only, data confirm earlier observations that IAP-associated antigens are expressed on the cell surface. There is no evidence that the Golgi apparatus is involved in the processing of IAP antigens in either cell type. (Author abstract) (31 Refs)

36. USE OF SEPHAROSE BEAD IMMUNOFLUORESCENCE ASSAY FOR COMPARISON OF THE TYPE D RETROVIRUSES MPMV AND PMFV.

Micheel B, Uckert W, Denner J, Fiebach H, Wunderlich V
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Arch Geschwulstforsch; 52(4):275-282 1982

Experiments using the Sepharose bead immunofluorescence assay (SBIFA) for comparing Mason-Pfizer monkey virus (MPMV) and a type D retrovirus isolated from a continuous human fibroblast line (PMFV) are reported. MPMV p27 related antigens were demonstrated in experiments using sandwich SBIFA and in those using competition SBIFA. The p15 of PMFV contained antigenic determinants not present in

MPMV. Both viruses reacted almost identically in the PMFV p27-specific assay, while there was no reaction of MPMV and a distinct reaction of PMFV in the PMFV p15-specific assay. (19 Refs)

37. EXPRESSION OF NORMAL LYMPHOCYTES OF TWO CELL SURFACE ANTIGENS, XENCSA AND G1X, RELATED TO THE MAJOR GLYCOPROTEINS (GP70) OF MURINE LEUKEMIA VIRUSES.

Morse HC, Taylor BA, Kozak CA, Chused TM, Sharrow SO, Hartley JW, Stockert E
Lab. Microbial Immunity, Natl. Inst. Allergy and Infectious Diseases, NIH, Building 5, Room 218, Bethesda, MD, 20205
J Immunol; 128(5):2111-2115 1982

XenCSA and GIX are two cell surface antigens related to the major envelope glycoproteins (gp70) of murine leukemia viruses. The levels of expression of these gp70 determinants were assessed in 36 recombinant inbred mouse strains and selected backcrosses derived from crosses between C57BL/6 with DBA/2 and C3H/He. These two antigens segregated in backcross mice and showed a different strain distribution pattern among the recombinant inbred mice, demonstrating that XenCSA and GIX are distinct genetic markers for different endogenous gp70 sequences. It was also shown that independent sets of genes regulate the expression of XenCSA and GIX. (Author abstract) (31 Refs)

38. TARGET CELLS INFECTED BY AVIAN ERYTHROBLASTOSIS VIRUS DIFFERENTIATE AND BECOME TRANSFORMED.

Samarut J, Gazzolo L
Rockefeller Univ., New York, NY, 10021
Cell; 28(4):921-929 1982

Transformation in vitro of bone marrow cells by avian erythroblastosis virus (AEV) gives rise to rapidly growing cells of erythroid nature. Target cells of neoplastic transformation by AEV are recruited among the early progenitors of the erythroid lineage, the burst-forming units-erythroid (BFU-E). They express a brain-related antigen at a high level and an immature antigen at a low level. We show that AEV-transformed cells express low levels of the brain antigen and high levels of the immature antigen. Their response to specific factors regulating the erythroid differentiation indicates that they are very sensitive to erythropoietin. Furthermore, cells transformed by a temperature-sensitive mutant of AEV differentiate into hemoglobin-synthesizing cells 4 days after being shifted to the nonpermissive temperature. All these properties are similar to those of late progenitors of the erythroid lineage, the colony-forming units-erythroid (CFU-E). These results indicate that the AEV-transformed cells are blocked in their differentiation at the CFU-E stage. (Author abstract) (36 Refs)

39. SUPPRESSION OF SPONTANEOUS MAMMARY TUMORIGENESIS DESPITE MTV-1 GENE EXPRESSION IN HYBRID AND BACKCROSS C3H-AVYFB X C3H/SM MICE.

Smith GH, Henry TJ, Vlahakis G, Arthur LO
Lab. Molecular Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):591-598 1982

Mouse mammary tumor virus (MMTV)-specific RNA and antigen content of normal and neoplastic mouse mammary tissue were measured in strains C3H/Sm and C3H-AvyfB in C3H-AvyfB female x C3H/Sm male F1 hybrids and in (C3H-AvyfB x C3H/Sm) x C3H/Sm male backcross segregants. The molecular data, along with the relative mammary tumor incidences, suggest that the endogenous MMTV provirus expression gene Mtv-1 present in C3H mice is fully expressed in the C3H-AvyfB subline but is silent or more probably absent in the C3H/Sm subline. Cessation of translational expression of endogenous MMTV occurred only in the agouti backcross females, suggesting an association between this phenomenon and the agouti locus of C3H/Sm. Evaluation of the relative MMTV RNA content of nucleic and cytoplasmic fractions from C3H/Sm mammary tissues strongly suggests that transport and/or processing of MMTV RNA is defective in these mice. This defect probably accounts for the absence of detectable MMTV antigens in C3H/Sm and agouti backcross mammary tissues and tumors and may contribute to the observed reduction in mammary tumor incidence. (27 Refs)

40. THE PERSISTENCE OF RETROVIRUSES.

Weiss RA
Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England
Symp Soc Gen Microbiol; 33:267-288 1982

Persistence of retroviruses (RV) in host populations (horizontal and vertical transmission; xenotropic endogenous viruses; interspecies transmission of RV; inheritance, expression, and possible functions of endogenous viral genes), antigen shift and drift, pathogenesis (apathogenic infections, acute neoplasms, slow neoplasms, auto-immune disease and anemia, neurological disease, and RV and human disease) are reviewed. RV are unique in their replicative cycle and perhaps in the most intimate form of viral persistence as host Mendelian traits. The viral oncogenes give insight into normal cell regulation and differentiation, and its perversion as cancer. (70 Refs)

41. P65 OF GAZDAR MURINE SARCOMA VIRUSES CONTAINS ANTIGENIC DETERMINANTS FROM ALL FOUR OF THE MURINE LEUKEMIA VIRUS (MULV) GAG POLYPEPTIDES (P15, P12, P30, AND P10) AND CAN BE CLEAVED IN VITRO BY THE MULV PROTEOLYTIC ACTIVITY.

Yoshinaka Y, Luftig RB
Dept. Microbiology, Mie Univ. Sch. Medicine, 174 Edobashi-2-Chome, Tsu, Mie 514, Japan
Virology; 118(2):380-388 1982

Thin-section electron micrographs of Gazdar murine sarcoma virus (Gz-MSV) particles showed that 100% of the particles possessed an immature morphology. Correspondingly, p65 (the major 65,000-dalton protein observed on sodium dodecyl sulfate-polyacrylamide gel electrophoresis for Gz-MSV particles) possessed antigenic determinants from all four of the murine leukemia virus (MuLV) Pr65gag polypeptides - that is, p30, p15, p12, and p10. This result is in contrast to earlier observations which reported that p65 lacked antigenic determinants of MuLV p10. It is consistent with the recent finding of Maxwell and Arlinghaus (1981) that Gz-MSV p65, when cleaved in vitro gives rise to a polypeptide with the size and antigenic determinant of MuLV p10. Thus, we suggest that Gz-MSV p65 should be designated as Gz-MSV Pr65gag. We also found that Gz-MSV Pr65gag could be cleaved in vitro by using a partially purified proteolytic factor that had been derived from Moloney murine leukemia virus (M-MuLV) by Sephadex G-75 column chromatography. Protein bands were produced that migrated on gels and had the same antigenic determinants as the MuLV intermediates Pr40gag (p30, p10) and Pr27gag (p15, p12). Pr55gag (p15, p12, p30), a minor compo-

nent, was also produced. Additional incubation of Gz-MSV Pr65gag led to a breakdown of the intermediate polyproteins into the four MuLV gag polypeptides p30, p10, p15, and p12. The final processing of Pr55gag and Pr40gag occurred more rapidly than that of Pr27gag. It thus seems that in vitro sequentially different processing events are involved in production of the four internal gag antigens from Gz-MSV Pr65gag. (Author abstract) (23 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

42. A MONOCLONAL ANTIBODY TO AN INTERSPECIES MAJOR HISTOCOMPATIBILITY DETERMINANT INHIBITS A VIRUS-SPECIFIC T-CELL CLONE.

Allouche M, Bennink JR, McKearn TJ, Doherty PC
(c/o Doherty), Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Cell Immunol; 68(1):193-198 1982

The cytotoxicity of an influenza-specific T-cell clone of BALB/c mouse origin for an H-2 compatible, virus-infected target is greatly inhibited by a monoclonal antibody which binds to mouse major histocompatibility complex (MHC) determinants, but was originally prepared against MHC antigens of the Brown Norway (BN) rat. The inhibition is still observed after absorption of the antibody with lymphoid cells from Lewis, but not from BN or Lewis 1N rats. It thus seems that the site blocked by this monoclonal antibody, which interacts with MHC antigens from a number of animal species, is at least close to a determinant on the MHC glycoprotein that is involved in T-cell recognition. This reagent may be useful for comparative analysis of the phylogeny of MHC-restricted T-cell responses in different species. (Author abstract) (18 Refs)

43. GENERATION OF CYTOTOXIC LYMPHOCYTES BY SV40-INDUCED ANTIGENS.

Chang C, Chang R, Mora PT, Hu C
Dept. Medical Res., Veterans General Hosp., Taipei, Taiwan, Republic of China
J Immunol; 128(5):2160-2163 1982

In order to study the correlation of in vivo tumor transplantation immunity and in vitro immunologic assays, cell-mediated cytotoxicity against SV40-transformed cells was studied in AL/N strain mice by using 51Cr-release assay. Killing of SV40-transformed AL/N fibroblast cells was observed by spleen cells of AL/N mice immunized with syngeneic SV40-transformed cells. Immunization with the solubilized SV40 tumor-specific transplantation antigen (TSTA) that induced transplantation immunity in vivo did not elicit cytotoxic spleen cells in vitro. However, the spleen cells from mice immunized with solubilized TSTA and then sensitized in vitro with SV40-transformed cells became cytotoxic against SV40-transformed fibroblasts. Similarly, SV40 TSTA (T antigen) purified by immunoprecipitation was able to prime the lymphocytes in AL/N mice: the primed lymphocytes could differentiate into cytotoxic lymphocytes upon in vitro stimulation by SV40-transformed cells. These data indicate that SV40 TSTA (T antigen) plays a role in the induction of cytotoxic lymphocytes. (Author abstract) (30 Refs)

44. PROPERTIES OF MOUSE LEUKEMIA VIRUSES. XVIII. EFFECTIVE TREATMENT OF AKR LEUKEMIA WITH ANTIBODY TO GP71 ELIMINATES THE NEONATAL BURST OF ECOTROPIC AKR VIRUS PRODUCING CELLS.

Fischinger PJ, Dunlop NM, Schwarz H, Ihle JN, Weinhold K, Bolognesi DP, Schafer W
Virus Control Section, NCI, Frederick, MD, 21701
Virology; 119(1):68-81 1982

To suppress spontaneous leukemia, treatment of AKR mice with antibody to the murine leukemia virus (MuLV) major glycoprotein (gp71) must commence during a narrow 'window' period between birth and Day 3. To examine the effect of treatment on virus expression, infectious MuLV cell centers (ICCs), free MuLV, and viral antigen presence were examined in various organs of control and antibody-treated neonatal AKR mice. The data graphically demonstrated that the treatment 'window' corresponded to a time just prior to the burst of ecotropic virus ICCs. The nature of ecotropic virus-positive cells and their elimination with treatment are discussed relative to later events in AKR leukemogenesis. (41 Refs)

45. EPSTEIN-BARR-VIRUS-SPECIFIC T-CELL MEMORY IN RENAL-ALLOGRAFT RECIPIENTS UNDER LONG-TERM IMMUNOSUPPRESSION.

Gaston JS, Rickinson AB, Epstein MA
(c/o Epstein)Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England
Lancet; 1(8278):923-925 1982

The level of long-term responsiveness of cytotoxic T cells to Epstein-Barr (EB) virus has been measured in peripheral-blood mononuclear-cell cultures from symptom-free renal-allograft recipients under conventional immunosuppression. Eight of 22 patients showed a profoundly impaired responsiveness when compared with healthy control donors. The allograft recipients as a group showed raised antibody titers to EB-virus capsid and early antigens, but within the group there was no clear relation between these antibody titers and the level of EB-virus-specific cytotoxic-T-cell function. These findings are particularly relevant to the pathogenesis of the malignant lymphomas to which renal-allograft recipients are unusually susceptible, in view of the evidence implicating EB virus. (Author abstract) (28 Refs)

46. P105, AN EBV-INDUCED TARGET OF THE IMMUNE RESPONSE (MEETING ABSTRACT)

Jones W, Casareale D, Reisert PS, Spiro RC, Sairenji T, Humphreys RE
University of Massachusetts Medical School, Worcester, MA, 01605
Fed Proc; 41(3):803 1982

In order to characterize EBV-induced targets of the immune response, a 00 dalton glycoprotein prominently recognized in immunoprecipitates of, Burkitt's lymphoma patients' sera with P3HR-1 EBV-superinfected Raji cells (S-Raji), was analyzed through the use of a specific heteroantiserum. Synthesis of p105 was restricted to EBV-superinfection and was not blocked with phosphonoacetic acid, indicating p105 to be an 'early' viral antigen. An external exposure of p105 on the cell surface was indicated by its glycosylation with radiolabeled sugars, by antibody binding in a radioimmunoassay with living cells and by membrane immunofluorescence. Although anti-p105 serum did not neutralize P3HR-1 virus (but bound to P3HR-1 cell membranes), it mediated antibody-dependent cel-

lular cytotoxicity (ADCC) to EBV-superinfected Raji and to control Raji cells but not to several EBV genome-negative cell lines. We conclude that p105 is an EBV-induced, external, glycosylated, early membrane antigen to which EBV-infected patients generate a substantial antibody response. These antibodies do not neutralize infectious virus but might mediate ADCC to, or otherwise affect, infected cells early in the virus cycle. (no Refs)

47. MONOCLONAL ANTIBODIES TO EPSTEIN-BARR VIRUS-INDUCED, TRANSFORMATION-ASSOCIATED CELL SURFACE ANTIGENS: BINDING PATTERNS AND EFFECT UPON VIRUS-SPECIFIC T-CELL CYTOTOXICITY.

Rowe M, Hildreth JE, Rickinson AB, Epstein MA
Dept. Pathology, Univ. Bristol Medical Sch., University Walk, Bristol BS8 1TD, England
Int J Cancer; 29(4):373-381 1982

Spleen cells from mice immunized with Epstein-Barr virus-transformed lymphoblastoid cells (EB-LCL) were used to generate monoclonal antibodies to cell surface antigens associated with the EB virus-transformed state. Radioimmune and immunofluorescence binding assays identified two antibodies, MHM6 and AC2, which reacted consistently with all EB-LCL tested, with a subpopulation of cells in some but not all EB virus genome-positive Burkitt lymphoma lines, but with none of a range of EB virus genome-negative cell lines of lymphoma or leukemia origin. While MHM6 appeared to bind an EB virus-related antigen, AC2 bound some other cell surface antigen which was also found on a small subpopulation of cells in lymphocyte cultures stimulated with phytohemagglutinin or with pokeweed mitogen. MHM6 and AC2 recognized single polypeptides with apparent mol wt of 45 kd and 80 kd respectively as shown by sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE) analysis of 125I-labeled cell surface polypeptides immunoprecipitated with these antibodies. These polypeptides were induced on experimentally-infected B cells within 24 hr of the expression of the EB virus nuclear antigen, EBNA, at a time known to coincide with the appearance of the lymphocyte-detected membrane antigen, LYDMA. However, saturating concentrations of MHM6 and of AC2 were unable to protect EB-LCL target cells from lysis by LYDMA-specific cytotoxic T cells in a chromium-release assay. (Author abstract) (50 Refs)

48. CELLULAR INTERACTIONS IN VITRO IN A PRIMARY ANTI-TUMOR RESPONSE.

Levy JP, Gomard E, Wibier-Franqui J, Herberman RB, Chang KS, Aoki T, Hashimoto Y
Laboratoire d'Immunologie et de Virologie des Tumeurs, Hopital Cochin, Paris, France
Excerpta Med Int Congr Ser; 576:268-281 1981

Factors affecting generation of mouse spleen cytotoxic T lymphocytes (CTL) against tumor cells carrying a virus-induced antigen closely related to the serologically defined FMR system (anti-FMR CTL) were investigated. Cytotoxicity was determined by 51Cr release. In vitro generation of primary anti-FMR CTL appeared to require the presence of a radioresistant, adherent, phagocytic, Thy 1-2-negative cell, probably a macrophage. These macrophages interacted with T cells because of Ia specificities. CTL activity was directed by the tumor cell H-2 specificity. This requirement for macrophages could be replaced by interleukin 2 (IL2), suggesting that macrophages may trigger IL2 production by presenting an Ia+ antigen to an anti-FMR helper T cell. Further work showed that Thy1-2 (+) primed helper T cells in the presence of normal macrophages triggered anti-FMR CTL from normal thymocytes. Lentinan (1 mg/kg days-7 to-2) increased CTL production, but not consistently. Other work suggests that Lentinan may increase the sensitivity of precursor CTL to IL2. (19 Refs)

49. CYTOTOXICITY AND SUPPRESSION DURING RADIATION AND RADLV-INDUCED LEUKEMOGENESIS (MEETING ABSTRACT)

Yefenof E, Kedar E
The Lautenberg Center for General and Tumor Immunology, Hebrew, University-Hadassah Medical School Jerusalem 91 010, Israel
Fed Proc; 41(3):417 1982

Adult C57BL/6 mice exposed to fractionated x-irradiation or inoculated with the highly leukemogenic variant of the Radiation Leukemia Virus (A-RadLV) develop high incidence lymphatic leukemias within 3-6 months. A-RadLV-induced, but not x-ray-induced lymphomas, can elicit cytotoxic responses in vitro in lymphocytes of preimmunized syngeneic mice, a reaction that is dependent on the expression of membrane associated viral antigenicity. As soon as 5 days after A-RadLV inoculation and during the entire leukemogenic process suppressor T cells are detectable in the spleen that are capable of specifically abrogating generation of syngeneic anti-tumor cytotoxic cells in vitro. These suppressor cells are generated directly by the virus, independently of initiation of the leukemogenic process. Mice exposed to fractionated x-ray irradiation or inoculated with the low leukemogenic D-RadLV variant do not develop suppressor cells and their splenocytes can be stimulated in vitro to generate cytotoxicity towards RadLV-induced leukemias. These findings suggest that: (a) although RadLV has been isolated from radiation induced leukemias, x-ray and RadLV-induced leukemogenesis do not seem to involve a common viral etiology; (b) induction of tumor specific suppression by A-RadLV may be essential for tumor progresson; and (c) the low leukemogenic potential of D-RadLV may be attributed to its inability to trigger host's suppressor cells. (no Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

50. INDUCTION AND TRANSPLANTATION OF MURINE SKIN CANCERS INDUCED BY METHOXSALEN PLUS ULTRAVIOLET (320-400 NM) RADIATION.

Kripke ML, Morison WL, Parrish JA
Cancer Biology Program, NCI-Frederick Cancer Res. Facility, P.O. Box B, Frederick, MD, 21701
JNCI; 68(4):685-690 1982

Properties of skin tumors resulting from treatment of mice with ip methoxsalen plus UVA (320-400 nm) radiation (PUVA) were compared to those of skin tumors induced by UVB (280-320 nm) radiation. Repeated treatment of C3H/HeN murine mammary tumor virus-negative (C3H-) mice with PUVA produced both fibrosarcomas and squamous carcinomas that were indistinguishable morphologically from UVB-induced tumors. Fragments of 12 primary PUVA-induced tumors were transplanted into normal and immunosuppressed syngeneic recipients, and all grew progressively. In contrast, 19 primary tumors induced by repeated exposure of C3H- mice to UVB grew only in the immunosuppressed mice and not in the

normal recipients. The growth of graded doses of cells from 5 PUVA-induced tumors was compared in normal and UVB-irradiated recipients. No preferential growth in UVB-irradiated mice was observed, even though this is characteristic of UVB-induced tumors. Thus PUVA-induced tumors do not appear to have the same antigenic properties as UVB-induced tumors. (Author abstract) (22 Refs)

51. STIMULATION OF ANTIBODY FORMATION IN IRRADIATED ANIMALS WITH ENDOGENOUS AND EXOGENOUS INTERFERON.

Zheleznikova GF
Central Res. Roentgeno-Radiological Inst., Leningrad, USSR
Radiobiologiia; 22(1):123-126 1982

The effect of interferon (IF) and IF inducers (IFI) on antibody formation was studied in mice irradiated with 400 or 500 rads. On day 1 after irradiation, animals were immunized with sheep RBC or with Escherichia coli vaccine. IF and IFI (Newcastle disease virus or complete antigen of E coli) were administered simultaneously with immunization. Irradiation resulted in marked inhibition of immune response to the antigens. Both endogenous IF caused significant stimulation of antibody-formation. Newcastle disease virus also enhanced the immune response of irradiated mice, while E coli endotoxin failed to stimulate the antibody formation. (9 Refs) (In RUS)

OTHER RELATED STUDIES

52. ABNORMAL MIGRATION OF T LYMPHOCYTE CLONES.

Dailey MO, Fathman CG, Butcher EC, Pillemer E, Weissman I
Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA, 94305
J Immunol; 128(5):2134-2136 1982

Several in vitro T cell clones were markedly deficient in their ability to home to peripheral lymphoid tissue. This was found for an alloreactive noncytolytic clone, a soluble antigen-(KLH)specific line, and cytotoxic clones specific for allogeneic cells and for Abelson virus-induced lymphoma cells. This abnormal circulation pattern was probably caused by the lack of the receptors of the lymphocytes for high endothelial venules (HEV), as implied by the lack of binding of these T cells to HEV in frozen sections of mouse lymph node and Peyer's patches. The loss of surface receptors that are necessary for normal lymphocyte migration may thereby alter the in vivo function of adoptively transferred T cells. (Author abstract) (18 Refs)

53. MONOCLONAL ANTIBODIES AGAINST THE T-CELL CHRONIC LYMPHOCYTIC LEUKEMIA-DERIVED CELL LINE, SKW3 (MEETING ABSTRACT)

Dowell BL, Gore I, McCormick GM, Metzgar RS
Department of Microbiology and Immunology, Duke University Medical Center, Durham, NC, 27710
Fed Proc; 41(3):270 1982

Splenocytes from BALB/C mice immunized with the human T-CLL cell line, SKW3, were fused with the P3 X63 Ag8 myeloma cell lines. Five cloned hybridomas were isolated which were cytotoxic for SKW3, but not for the common acute lymphoblastic leukemia-derived (cALL) cell lines, REH and 697. DU-SKW3-1 is an IgG2b antibody which detect a 65-68,000 dalton antigen present on all peripheral blood T lymphocytes and thymocytes, but absent from normal B lymphocytes, monocytes, granulocytes, and platelets. The antigen was also detectable on T-cell derived leukemias and lymphomas and on B-cell derived CLL cells, but not on myeloid leukemias or on common ALL cells. The epitope detected by DU-SKW3-1 is different from that detected by L17F12. DU-SKW3-2 reacts with a trypsin-sensitive antigen which is preferentially expressed on mature T and B lymphocytes. It was cytotoxic for EBV (Epstein-Barr virus)-transformed B cell lines, myeloma cell lines and HuT78, a Sezary-derived cell line. DU-SKW3-2 was not cytotoxic for four T-ALL derived cell lines or for four cALL-derived cell lines. The monoclonals, DU-SKW3-3,4, and 5 were cytotoxic for normal T cells, B cells and monocytes, but did not react with cALL cell lines. (no Refs)

54. EBV-IGA AND NEW HETEROPHILE ANTIBODY TESTS IN DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS.

Evans AS, Niederman JC
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
Am J Clin Pathol; 77(5):555-560 1982

An evaluation has been made of the EBV-IgA tests and the immune adherence hemagglutination assay (IAHA) as compared with standard diagnostic procedures in 119 serial sera from 22 clinical and 113 sera from 42 subclinical cases of EBV infectious mononucleosis. EBV-IgA antibody was demonstrable in 86.4% of patients using EB3 cells as antigen and in 68.2% with P3/HRIK cells. For heterophile antibody the IAHA test was more sensitive, gave higher titers, and was positive longer than the standard absorbed horse or sheep RBC tests in both clinical and subclinical EBV infections. (Author abstract) (16 Refs)

55. HUMAN PLASMACYTOMA WITH AN UNUSUAL KARYOTYPE GROWING IN VITRO AND PRODUCING LIGHT-CHAIN IMMUNOGLOBULIN.

Karpas A, Fischer P, Swirsky D
Dept. Haematological Medicine, Cambridge Univ. Clinical Sch., Cambridge, England
Lancet; 1(8278):931-933 1982

A new human plasmacytoma line (Karpas 707) was established from the cells of the bone-marrow and peripheral blood of a patient with Bence-Jones-positive multiple myeloma. The cells of this new line resembled the patient's malignant cells and fresh myeloma cells from nine other patients in being Epstein-Barr viral nuclear antigen negative. They looked like plasma cells and they secreted only lambda light chains. Both these cells and the patient's fresh cells were hypodiploid and contained the Philadelphia chromosome and several other markers. This line seems to be the first human plasmacytoma line since the IgE lambda-producing line (U266) established in 1968, and it may be suitable for the production of human monoclonal antibodies. (Author abstract) (14 Refs)

56. LYMPHOCYTE COUNT AND DELAYED CUTANEOUS HYPERSENSITIVITY IN PATIENTS WITH BREAST CARCINOMA (MEETING ABSTRACT)

Lee YT
Department of Surgery, University of Southern California School of Medicine, Los Angeles, CA, 90033
Proc Am Soc Clin Oncol; 1:C-169 1982

The usual method of measuring cell mediated immune response in patients is by delayed cutaneous hypersensitivity (DCH) reaction to microbial or viral antigens. We have studied the inter-relationship of DCH response and peripheral blood lymphocyte counts in 124 patients with breast carcinoma (40 stage I; 32 II; 23 III; 29 IV). Blood samples were obtained before the administration of seven DCH recall antigens: PPD (purified protein derivative), Monilia, histoplasmin, mumps, Coccidioidin, streptokinase-streptodornase, and trichophytin. DCH responses were scored according to the recommendations of Bates et al. Among the seven DCH antigens tested, there are significantly higher numbers of lymphocyte counts among patients with higher scores of reactivity against PPD, mumps and coccidioidin. If one uses the number of positive DCH reactions, patients who reacted to 3-7 recall antigens had significantly higher lymphocyte counts than those who reacted to two or less antigens. (1 Ref)

57. BLA: A BURKITT LYMPHOMA-ASSOCIATED ANTIGEN DEFINED BY A MONOCLONAL ANTIBODY (MEETING ABSTRACT)

Lipinski M, Wiels J, Fellous M, Tursz T
Institut Gustave-Roussy, 94800 Villejuif, France
Fed Proc; 41(3):726 1982

A rat monoclonal IgM antibody (38-13) has been raised against Daudi cells, derived from a Burkitt lymphoma (BL). This antibody defined an antigen, referred to as BLA, specifically expressed on Burkitt tumor cells, whether they contain the Epstein-Barr virus (EBV) genome or not. BLA is not detected on EBV-positive lymphoblastoid cell lines, normal or mitogen activated lymphocytes, or fresh malignant cells from patients affected with various non-BL lymphoproliferative disorders. Therefore, 38-13 recognizes a BL-associated antigen clearly not related to EBV. Biochemical analysis indicates that BLA is a hydrophobic glycoconjugate: the antigen resists proteolytic treatments; no specific protein is detected by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) analysis after precipitation of radio-labeled BL membranes with 38-13; the antibody is specifically absorbed by a chloroform-methanol extract of BL cells; immunofluorescence staining for BLA is inhibited in the presence of D-galactose, N-acetylneuraminic acid and N-acetyl D-galactosamine. Since it displays an apparent specificity for BL cells, the 38-13 monoclonal antibody could represent a valuable tool for diagnosis and specific immunotherapy of BL. (no Refs)

58. PROBIOTICS: NONANTIGENIC TISSUE FRACTIONS IN CANCER CONTROL.

Nutini LG, Sperti GS, Fardon JC, Duarte AG, Freidel JF
St. Thomas Inst., 1842 Madison Road, Cincinnati, OH, 45206
J Surg Oncol; 19(4):233-237 1982

The effects of probiotics, nonantigenic fractions of normal and malignant cells on tumors, and of similar fractions of normal cells on bacteria and viruses are discussed. The effects are considered in relation to tumor growth and development. In a control group of mice given sc inoculations only of viable dbrB tumor cells in DBA/1 mice, 100% developed tumors. In a group receiving sc and iv injections of tumor cells and given the tumor fractions, 20% developed lung tumors and 53% developed sc tumors. In an experiment in which mice received only iv injections of viable tumor cells and the tumor fractions, 100% of the controls died with no death occurring in the treated group. It is concluded that nonantigenic cellular fractions (probiotics) effective in inducing resistance to some bacterial and viral diseases are effective in inducing resistance to tumors in an inbred strain of mice. (Author abstract) (25 Refs)

59. SEROLOGICAL ANALYSIS OF CELL SURFACE ANTIGENS ON METHYLCHOLANTHRENE-INDUCED MOUSE SARCOMAS WITH ANTISERA PRODUCED AGAINST THE TUMORS.

Tanimoto M, Takahashi T, Nishizuka Y
(c/o Takahashi) Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Tashiro-cho, Chikusa-ku, Nagoya 464, Japan
Gan; 73(2):184-192 1982

Out of nine cell lines from methylcholanthrene-induced fibrosarcomas in BALB/c, four lines without expression of murine leukemia virus (MuLV) were selected for immunization of three different F1 hybrids with mitomycin C-treated in vivo sarcoma cells. Antibody activity was tested by immune adherence (IA) and protein A (PA) assays after the eighth immunization. Two sarcomas, CMC-11 and CMC-12, produced antibodies detectable by IA in (BALB/c x C3H/He)F1, but no antibodies were detected by PA. (BALB/c x C3H/He)F1 anti-CMC-11 was tested against CMC-11 and three other MuLV-sarcomas as well as against the skin fibroblast (C-11) from a BALB/c mouse, in which the primary CMC-11 sarcoma was induced. CMC-11 line reacted up to 1/80, but other lines were weakly positive or negative. Absorption analysis showed that the antigen defined by anti-CMC-11 was present on CMC-11 as well as on many other sarcoma cell lines, but not on BALB/c thymocytes and spleen cells, nor on leukemia and myeloma cells. Among five fibroblast cultures tested, C-14 showed complete absorption. It seems significant that only C-14 produced tumor nodules in BALB/c mice, in contrast to four other fibroblast cultures. This suggested that this antibody was directed against antigens present on transformed fibroblasts and sarcoma cells. The specificity of (BALB/c x C3H/He)F1 anti-CMC-12 serum indicated that this antiserum also seemed to detect transformation-related antigens, although it showed a broader specificity with regard to the tissue representation detected. (Author abstract) (29 Refs)

60. STUDIES ON ANTIGENS OF A LEUKEMIC NULL-CELL LINE (NALL-1). I. STIMULATORY CAPACITY IN MIXED LYMPHOCYTE CULTURE.

Uno J
Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan
Okayama Igakkai Zasshi; 93(5/6):481-487 1981

A one-way mixed lymphocyte reaction between lymphocytes from normal human donors and mitomycin C-treated cells from a human leukemic null-cell line (NALL-1) was investigated. Human leukemic T-cell and B-cell lines, an Epstein-Barr virus (EBV)-negative Japanese Burkitt's lymphoma line, and two EBV-positive normal B-cell lines were studied in parallel. Normal lymphocytes were stimulated significantly by the cultured null- and B-cells but not by the cultured T-cells. The stimulatory capacity of this null-cell line was approx equal to that of the leukemic, lymphoma, and normal B-cell lines, and was unrelated to the presence of complement receptor, surface

immunoglobulin, EBV-associated nuclear antigen, terminal deoxynucleotidyl transferase or the origin of the cell lines. These results suggest that not only leukemic B-cells but also leukemic null-cells have stimulatory determinants in mixed lymphocyte culture. (Author abstract) (21 Refs) (In JPN)

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OCTOBER, 1982

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. HEPATITIS B AND PREVENTION OF HEPATOCELLULAR CARCINOMA.

Blumberg BS

Inst. for Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111

Nouv Presse Med; 11(12):903-905 1982

The role of a hepatitis B virus (HBV) vaccine in the prevention of hepatocellular carcinoma (HCC) is discussed. Production of the HBV vaccine, the relationship between HBV and HCC, and viruses similar to HBV are considered. Geographic regions with a high incidence of HBV surface antigen coincide with areas of high HCC incidence. Infection with HBV is most common among patients presenting with HCC compared to appropriate controls. (no Refs) (In FRE)

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2. EVIDENCE THAT HEPATITIS B VIRUS HAS A ROLE IN LIVER-CELL CARCINOMA IN ALCOHOLIC LIVER DISEASE.

Brechot C, Nalpas B, Courouce AM, Duhamel G, Callard P, Carnot F, Tiollais P, Berthelot P
Unite de Recombinaison et Expression Genetique, Institut Pasteur, 28 rue du Docteur Roux, 75015 Paris, France
N Engl J Med; 306(23):1384-1387 1982

Determinations of hepatitis B virus (HBV) DNA were made in a prospective study of 51 alcoholics without hepatocellular carcinoma (HCC) and in a retrospective study of 20 alcoholics with both alcoholic cirrhosis and HCC. The overall prevalence of HBV serologic markers was 37% in the first group, compared with 10% in a nonselected blood-donor population. HBV DNA was detected in liver samples from three hepatitis B surface antigen (HBsAg)-positive patients from the first group and in liver samples of five other patients from this group in whom serum HBsAg was not detectable. In the second group, HBV DNA was detected in the neoplastic portion of the autopsied liver in all patients. Integration of viral DNA into the hepatocellular DNA was demonstrated in the samples from the second group, but conclusively in only two samples from the first group. HBV DNA was not detected in the livers of 14/16 patients with alcoholic liver disease (from the first group) who were negative for HBsAg but positive for anti-hepatitis B core antigen or anti-HBsAG, suggesting that HBV is probably not involved in progression of the liver disease. The presence of HBV DNA in livers of alcoholic patients without HCC may delineate the population at high risk for development of this disease. (25 Refs)

3. HEPATITIS B E ANTIGEN AND ANTIBODY TO HEPATITIS B E ANTIGEN IN THE PATIENTS WITH PRIMARY HEPATOCELLULAR CARCINOMA (MEETING ABSTRACT)

Fukuda Y
2nd Department of Internal Medicine, Kyoto University School of Medicine, Kyoto, Japan
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

A close association between heptitis B virus (HBV) infection and primary hepatocellular carcinoma (HCC) has been noted. Therefore, to gain further insight into this relationship, we undertook the present study. First, we looked for the prevalence of HBeAg and antibody to HBeAg (HBeAb) in the patients with HCC and compared the results in asymptomatic carrier (ASC), chronic hepatitis (CH) and liver cirrhosis (LC). Second, the serial detection of HBeAg/HBeAb system was done retrospectively in the sera from the patients who were HBsAg-positive chronic liver disease and progressed to HCC. Sera of 73 patients with HBsAg-positive HCC were tested for HBeAg and HBeAb. HCC was diagnosed histologically either by liver biopsy or autopsy, or by increased alpha-fetoprotein (AFP) levels, liver scan, CT (computed tomography) scan, and celiac angiography. The control consisted of 76 patients with ASC, 101 patients with CH and 50 patients with LC. Twenty six of 73 (36%) patients with HCC were positive for HBeAg and 25 (34%) were positive for HBeAb. Positive frequency of HBeAg in the patients with ASC, CH and LC were 29%, 48% and 50% respectively. We have done the retrospective determination of HBeAg and HBeAb in sera from 11 patients with HCC who were followed as liver cirrhosis for more than 3 years. Nine of 11 patients showed persistent HBeAg-positive state throughout their clinical course and 2 of 11 showed persistent HBeAg-positive state until about 1.5 years and 2 months before occurrence of HCC respectively. (no Refs)

4. REACTIVATION OF CHRONIC HEPATITIS B VIRUS INFECTION BY CANCER CHEMOTHERAPY (MEETING ABSTRACT)

Hoofnagle JG, Dusheiko GM, Schafer DF, Micetich KC, Young RC, Costa J
National Institutes of Health, Bethesda, MD
32nd Annual Meeting of the American Association for the Study of Liver Diseases, November 5-8, 1981, Chicago, Illinois. American Association for the Study of Liver Diseases 97 pp., 1981.

Two patients referred for cancer chemotherapy were found to be chronic asymptomatic hepatitis B surface antigen (HBsAg) carriers at initial presentation. They had normal serum bilirubin, albumin and aminotransferase levels. Their sera were positive for HBsAg but were negative for hepatitis B e antigen (HBeAg) and hepatitis B virus specific DNA and DNA polymerase activity. Both patients were positive for antibody to HBeAg (anti-HBe). Liver biopsy in one patient revealed normal hepatic architecture and many 'ground glass' hepatocytes. The first patient was treated with cyclophosphamide, actinomycin, bleomycin, vincristine and cis-platinum for testicular carcinoma. The second was given cyclophosphamide, vincristine, prednisone and procarbazine (C-MOPP) for nodular mixed lymphoma. Both patients developed acute, icteric hepatitis within three months of starting cycled chemotherapy. This appeared to be due to a reactivation of type B hepatitis, in that both cases were accompanied by a marked increase in HBsAg titer and the appearance of hepatitis B virus DNA and DNA polymerase in the serum. Neither patient had received blood transfusions and both remained negative for antibody to hepatitis A virus. The two patients recovered. One eventually became HBsAg negative and developed antibody to HBsAg (anti-HBs). The second patient developed a second bout of severe acute hepatitis accompanied by the reappearance of hepatitis B virus DNA and DNA polymerase as well as HBeAg after a second course of chemotherapy. (no Refs)

5. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K
Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan
Nippon Rinsho; 40(2):468-477 1982

World epidemiological surveys and molecular biology research on the relationship between hepatitis B virus (HBV) and liver cancer are discussed, and cases of hepatitis and hepatic cirrhosis which transformed into hepatic cancer in Japanese patients are analyzed. Various epidemiological and molecular biology studies show a clear correlation between HBV and hepatic cell carcinoma. Patients with B-type hepatitis, cirrhosis, or hepatic cancer were significantly younger than those with non-B type hepatitis, cirrhosis, or hepatic cancer, respectively. Approx 70% of 110 cases of hepatic cancer were found to have positive laboratory findings related to HBV. The patients who had chronic liver disease and who were positive for hepatitis Bs (HBs) antigen were thought to be at high risk for developing hepatic cancer. No direct relationship was observed between alpha-fetoprotein (AFP) levels and serum HBs antigens, however, monitoring levels of AFP was thought to be an important method to help detect early stage liver cancer. (33 Refs) (In JPN)

6. OF WOODCHUCKS AND MEN: THE CONTINUING STORY OF HEPATITIS B AND HEPATOCELLULAR CARCINOMA.

Johnson PJ, Williams R
Liver Unit, King's Coll. Hosp. Medical Sch., London SE5 8RX, England
Br Med J; 284(6329):1586-1588 1982

Statistical evidence that presence of hepatitis B surface antigen (HBsAg) is associated with high rates of hepatocellular carcinoma is presented. Studies on the relationship between HBsAg and cirrhosis lead to the hypothesis that in susceptible people the hepatitis B virus causes either a healthy carrier state or chronic liver disease depending on the host's immunological reaction to the virus. After many years the virus becomes part of the host genetic material, and in some cases this may lead to malignant change. Potential uses of vaccines against hepatitis B virus or antiviral chemotherapy in carriers are discussed. (22 Refs)

7. ALPHAFETOPROTEIN LEVELS MEASURED BY RADIOIMMUNOASSAY IN VARIOUS LIVER MALIGNANCIES.

Chang FY, Chen TC, Fong MS, Lin S, Yeh SH
Div. Gastroenterology, Tri-Service General Hosp., Taipei, Taiwan
Taiwan I Hsueh Hui Tsa Chih; 81(2):224-231 1982

Alpha-fetoprotein (AFP) levels in 114 patients with primary hepatocellular carcinoma (HCC), 11 patients with cholangiocarcinoma, and 17 patients with metastatic liver cancer were determined by radioimmunoassay, and compared with similar determinations in 44 adults with normal liver function. AFP levels in the healthy subjects never exceeded 20 nano(n)g/ml; 39 determination were less than 10 ng/ml. Of the 142 cancer patients, 93/114 HCC, 3/11 cholangiocarcinoma, and 2/17 metastatic liver cancer patients had AFP levels greater than 20 ng/ml. Rates of elevation of AFP in cancer patients seemed to decrease with increasing patient age, but the relationship as not statistically significant. Among 75 hepatitis B surface antigen (HBsAG)-positive patients, 86.7% had AFP levels greater than 20 ng/ml. Of 15 HBsAg-negative HCC patients, 66.7% had AFP levels greater than 20 ng/ml. The relation of HBsAg-positivity to elevated AFP level was not statistically significant. More than half of the HCC patients had AFP level greater than 320 ng/ml, but not all HCC patients had elevated AFP due to lower secretion. The relationship of HCC to HBsAg-positivity may be causal in this Taiwanese population, in which both hepatitis B infection and HCC are common. (32 Refs)

8. HEPATITIS-B VIRUS INFECTION IN BLACK CHILDREN WITH HEPATOCELLULAR CARCINOMA.

Kew MC, Hodkinson J, Paterson AC, Song E
Dept. Medicine, Witwatersrand Univ. Medical Sch., Hospital Hill, Johannesburg 2001, South Africa
J Med Virol; 9(3):201-207 1982

Six unselected South African black children (2 female, 15 and 16 yr old; 4 male, 10-13 yr old) with hepatocellular carcinoma (HCC) were examined for hepatitis-B virus (HBV) infection. Characteristics of the tumors were similar to those in black adults. All of the patients were positive for hepatitis B surface (HBs) antigen and hepatitis B core antigen in the serum. Hepatitis Be antigen was present in four patients; sera from the two patients without e antigen (1 male, 1 female) were positive for e antibody. All of the sera were negative for HBs antigen. Taken in conjunction with the HBV status of black adults in South Africa, the findings suggest the possibility that nearly all black patients with HCC are or have been infected with HBV. If HBV is oncogenic, tumor formation may occur within 10 yr of the initial infection. (14 Refs)

9. CLINICAL AND IMMUNOLOGICAL ASPECTS OF HEPATITIS B VIRUS INFECTION IN CHILDREN WITH HAEMATOLOGICAL MALIGNANCIES.

Koscielniak E
Dept. Hematology, Pediatric Clinic, Medical Acad., Wronskiego 11, 50-372 Wroclaw, Poland
Arch Immunol Ther Exp (Warsz); 29(5):689-695 1981

One hundred forty three patients with hematological malignancies were screened at the onset and during the disease for hepatitis B surface antigen (HBsAg) in the serum. HBsAg was found in serum of 38/143 patients (26.5%) in a mean period of 14.5 mo after the diagnosis was established. The relationship between immunological status of the patients and the course of the infection was analyzed. In 17/38 patients who developed icteric hepatitis, the mean amounts of E-rosetting lymphocytes were significantly higher than in the anicteric hepatitis group and asymptomatic HBsAg carriers. These two groups of patients showed a tendency to persistence of HBsAg and developing of chronic carrier state or chronic hepatitis. (Author abstract) (19 Refs)

10. HEPATITIS B VIRUS INFECTION IN HEPATOCELLULR CARCINOMA AND OTHER MALIGNANCIES (MEETING ABSTRACT)

Lim KP, Singh R, Oon CJ
University Department of Medicine, National University of Singapore, Singapore General Hospital, Singapore 0316, Singapore
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Patients with advanced malignant diseases have depressed cell mediated immunity and are vulnerable to various viral and opportunistic infections. Similarly patients with primary hepatocellular carcinoma (PHC) are also known to have a depressed immunity. Seropositive Hepatitis B virus (HBV) infections are common (70-90%) in PHC patients in the Asian Pacific Region and this country. Could this presence of the HBV in such PHC patients be due to a newly acquired HBV infection from a depressed immunity of malignancy or to a pre-existing infection by the HBV virus? We investigated this question in a pilot study on 56 PHC patients and 47 patients with other malignancies. During the period between January to July 1980 the sera of these patients and a random normal control group matched for age and sex were examined. Hepatitis B surface antigen (HBsAg) and antibody to Hepatitis B core antigen (HBcAb) were determined using commercial radioimmunoassay kits. In this study the incidence of HBs antigenemia in PHC patients was found to be higher than in normal individuals or in the tumor control group. In the latter two groups, the incidence of antigenemia was similar. The incidence of HB core antibody was also higher in PHC patients than in normal controls but not significantly different from the other tumor controls. (no Refs)

11. HISTOLOGIC GROWTH PATTERN OF HEPATOCELLULAR CARCINOMA: RELATIONSHIP TO ORCEIN(HEPATITIS B SUkFACE ANTIGEN)-POSITIVE CELLS IN CANCER TISSUE.

Nakashima T, Kojiro M, Kawano Y, Shirai F, Takemoto N, Tomimatsu H, Kawasaki H, Okuda K
(c/o Okuda) First Dept. Medicine, Chiba Univ. Hosp., Chiba 280, Japan
Hum Pathol; 13(6):563-568 1982

The histologic pattern of tumor growth at tumor-nontumor boundaries was studied in 60 livers bearing hepatocellular carcinoma. Three growth patterns, arbitrarily described as 'sinusoidal,' 'replacing,' and 'encapsulated,' were distinguished. Cancer cells growing in the sinusoids between liver cell cords (sinusoidal pattern) were anaplastic; those growing in an expansile fashion and acquiring a fibrous capsule (encapsulated pattern) were most differentiated; and those growing into the cord of liver cells and replacing them (replacing pattern) were differentiated to an intermediate degree. There was certain relation between the histologic growth patterns and gross morphologic features of the tumors. Test results for 20 of the 60 cases were positive for serum hepatitis B surface antigen (HBsAg), and the livers also contained orcein-positive cells. Orcein-positive cells were frequently seen at the border between tumor and parenchyma. Cells containing HBsAg as an orcein-positive inclusion were present in cancer tissue in three cases. When serial sections were made from such areas and stained alternately with hematoxylin and eosin and orcein, it was found that these cells were hepatocytes blended with cancer cells. This phenomenon was related to the growth pattern of tumor cells. Orcein-positive cells were never found in metastatic lesions. (Author abstract) (28 Refs)

12. EARLY STAGE CANCER DIAGNOSIS SYSTEM FOR MINUTE HEPATOCELLULAR, CHOLEDOCHAL, AND PANCREATIC CANCERS: CURRENT CAPABILITIES AND PROBLEMS.

Okuda K, Tsuchiya Y, Saisho H
First Dept. Internal Medicine, Chiba Univ. Sch. Medicine, Chiba, Japan
Nippon Rinsho; 40(1):146-150 1982

Patients at high risk for hepatic, choledochal, or pancreatic cancer and methods used in early detection of minute cancers are discussed. Patients at high risk of hepatic cancer include those with hepatic cirrhosis and who are positive for hepatitis B-virus surface antigen (HBsAg), those with a history of HBsAg negative cirrhosis and had transfusions or surgery, those with a long history of chronic hepatitis, and those with Budd-Chiari disease. Methods used to diagnose early stage hepatocellular cancer include testing for alpha-fetoprotein, ultrasonography, computed tomography, 99mTc scintigraphy, and abdominal angiography. Choledochal cancer has been primarily detected with choledochal roentgenography, but real time ultrasonography is being used more often. Ultrasonography is useful in detecting eruptive-type gall bladder cancers but not the flat-type. Gall bladder tumors greater than 10 mm can be diagnosed as malignant, and the 8-10 mm tumors are potentially malignant. When roentgenograms are negative for gall bladder disease, ultrasound-guided puncture biopsy might be performed. Distinctive features of pancreatic cancers observed with the aid of ultrasonography include an enlarged localized tumor, a low-echo localized within the parenchyma or an inconsistent echo level in a spherical shape, and numerous spherical dilations of the pancreatic duct. (8 Refs) (In JPN)

13. A STUDY OF THE RELATIONSHIP BETWEEN THE PROGNOSIS OF CHORNIC ACTIVE HEPATITIS AND THE HBV ASSOCIATED ANTIGEN/ANTIBODY SYSTEMS (MEETING ABSTRACT)

Takase K, Tameda Y, Kosaka Y
First Department of Medicine, Mie University Hospital, Tsu, Japan
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Our series consisted of 31 patients admitted to our clinic and diagnosed as chronic active hepatitis (CAH) over the period of 12 years from January 1, 1969 until December 31, 1980. The diagnosis was based on liver histology in all these patients, who were then followed up with liver biopsy performed subsequently at an interval of more than a year. Determination were made by RIA (radioimmunoassay) methods of HBsAg, anti-HBs, HBeAg, anti-HBe anti-HBc in blood serum taken from each patient on initial and final liver biopsy. The serum specimen were kept frozen at-20C until time of use. An attempt was made to examine the relationship between the HBV (hepatitis B virus)-associated antigen/antibody systems so determined and the prognosis of chronic hepatitis based on follow-up liver biopsy. On initial liver biopsy 5 of 13 patients with CAH with spotty or focal necrosis were HBsAg positive, as 5 of 7 patients with sublobular necrosis and 7 of 11 patients with lobular disorganization. Most of HBsAg negative patients were anti-HBs or anti-HBc positive: HBV-associated antigen or antibody was completely undetectable in only 4 of these 31 patients. There was no difference in the frequency of progression to liver cirrhosis (LC) between 17 HBsAg positive patients with CAH. On the other hand, progression to LC occurred in only 1 of 8 HBeAg negative patients, compared to 5 of 10 HBeAg positive patients, who were HBsAg positive. There were 5 patients who were HBeAg positive initially but then become HBeAg negative in the course of observation. (no Refs)

14. DETECTION OF ANTI-HBC (HEPATITIS B CORE ANTIBODIES) AND ITS CLINICAL SIGNIFICANCE.

Wang Q, Shi X, Wang D, Chou D, Yang Y, Zhang X, Jiang W, Chen H, Xu C, Zou W
Dept. Infectious Diseases, Affiliated Ruijin Hosp., Shanghai Second Medical Coll., Shanghai, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(3):194-197 1981

Using partially purified hepatitis B core antigen, the anti-HBc was analyzed in 202 normal subjects and 600 patients including 424 with various types of hepatitis, 145 symptomless HBsAg carriers, 8 with liver cirrhosis and 23 with liver cancer. Results showed that highest infection rate of hepatitis B virus (HBV) occurred in the hepatitis patients (67.2-99%), while in patients with liver cirrhosis and liver cancer the HBV infection rates were 75% and 56.6% respectively, as compared to 8.4% in normal subjects. (11 Refs) (In CHI)

15. LIVER CELL DYSPLASIA IN ASSOCIATION WITH HEPATOCELLULAR CARCINOMA AND CIRRHOSIS IN HONG KONG (MEETING ABSTRACT)

Wu PC, Ho JC, Mak TK, Lai CL, Gibson JB
Department of Pathology, University of Hong Kong, Hong Kong, Hong Kong
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Necropsy and biopsy materials from Chinese patients with cirrhosis, hepatocellular carcinoma (HCC) or HCC associated with cirrhosis admitted into Queen Mary Hospital, Hong Kong were studied. Liver cell dysplasia was found in 337 of 558 post-mortem cases of cirrhosis and in 203 of 309 cases of HCC. It was significantly more frequently identified in livers showing both cirrhosis and HCC than in livers showing HCC alone or cirrhosis only. Applying Bayes' theorem, the risk facing dysplasia-positive Chinese males in developing HCC was calculated. For Chinese male non-cirrhotics with liver cell dysplasia at necropsy, compared with male non-cirrhotics without dysplasia, the approximate risk factor for HCC is 13:1, whereas the male cirrhotics with liver cell dysplasia, compared with male cirrhotics without dysplasia, the risk for HCC is approximately 2:1. A significant correlation was also found between liver cell dysplasia and the presence of hepatitis B surface antigen (HBsAg) in the livers. In the presence of dysplasia, the risk for HCC is increased two-fold in males who are also HBsAg-positive. Therefore the presence of liver cell dysplasia in both cirrhotic and non-cirrhotic Chinese males carries a significantly higher risk of developing HCC, and the risk is even greater in those who are HBsAg-positive. (no Refs)

16. HEPATITIS VACCINATION.

Zachoval R, Deinhardt F
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Z Gastroenterol; (Special17):110-116 1982

Two double-blind studies with placebo controls indicate that a hepatitis B vaccine consisting of hepatitis B surface antigen particles is safe and effective in preventing hepatitis B infections. Hepatitis B may act as a cocarcinogen in primary hepatic carcinoma. No serious side effects of the vaccine were noted; use of the vaccine is therefore appropriate for high-risk groups. Patients at high risk should be actively immunized; active-passive immunization should be used when immediate protection is required. (23 Refs) (In GER)

17. CANCER: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS FOR THE 1980S. VOLUME 1.

Burchenal JH, Oettgen HF
Memorial Sloan-Kettering Cancer Center, New York, NY
Cancer: Achievements, Challenges, and Prospects for the 1980s. Volume 1. New York, Grune and Stratton, 685 pp., 1981.

The current status of cancer research and prospects for the future are reviewed. Topics include epidemiology (analytic epidemiology, epidemiology and cancer control policy), viruses (polyoma, feline leukemia, sarcoma, Epstein-Barr viruses, retroviruses), radiation hazards (radiation and thyroid, breast, and childhood cancers), industrial and lifestyle carcinogens (metabolic activation of chemical carcinogens, tumor registries), host defense against cancer (immunogenetics of cancer in man and animals, cell-mediated immune reactions to human cancer antigens and their regulation, biochemistry of human tumor antigens), genetics (genetic epidemiology of human cancer, specific fine structural chromosome defects in human neoplasia, clinical features and management of genetic cancers), cell biology and cancer (evolution of the malignant cell phenotype, properties of metastatic tumor cells), prevention of carcinogenesis (inhibitors of chemical carcinogens, advances in the use of retinoids for cancer prevention, blocking of tumor promotion by protease inhibitors), and advances in diagnosis (biochemical and immunologic diagnosis of cancer, advances in nuclear imaging, early diagnosis of liver cancer, advances in diagnosis of gastrointestinal neoplasms). (1641 Refs)

18. FREQUENCY AND DISTRIBUTION OF PAPILLOMAVIRUS ANTIGENS IN CERVICAL DYSPLASIA AND CARCINOMA IN SITU (MEETING ABSTRACT)

Kurman RJ, Lancaster WD, Jenson AB
Department of Pathology and Obstetrics and Gynecology, Georgetown University Hospital, Washington, DC
Lab Invest; 46(1):46A 1982

Two hundred and ninety-three cases of cervical dysplasia (139 mild, 72 moderate, 44 severe) and carcinoma in situ (CIS) (38) retrieved from the surgical pathology files of Georgetown University Hospital from 1974 to 1977, were screened for the presence of papillomavirus (PV) antigens, using a peroxidase-antiperoxidase technique, having immunospecificity against the genus-specific (common) antigens of the papillomaviruses on formalin-fixed paraffin-embedded tissue. A positive reaction for PV antigens was found in 68 mild dysplasias, 13 moderate dysplasias, six severe dysplasias, and three CIS. Positive cells were focally or less commonly diffusely distributed in the superficial and intermediate layers of the epithelium in areas of mild or moderate dysplasia and also associated with or immediately adjacent to areas of severe dysplasia and CIS. The positive reaction, invariably intranuclear, was present in nuclei with wrinkled nuclear membranes that were rounded, ovoid, or flattened. Positive cells with flat or ovoid nuclei were mononuclear with scant cytoplasm, whereas those with rounded nuclei were sometimes binucleate and characteristically contained clear cytoplasm. Cells with similar morphologic features to those showing a positive reaction of PV antigens were frequently negative but were also considered as showing wart virus atypia. Cells showing wart virus atypia, irrespective of being PV-positive or negative, were found in 126 mild dysplasias, 51 moderate dysplasias, 24 severe dysplasias, and 10 CIS. (no Refs)

19. MURINE MAMMARY TUMOR VIRUS-RELATED ANTIGEN IN HUMAN MALE MAMMARY CARCINOMA (MEETING ABSTRACT)

Lloyd RV, Rosen PP, Sarkar NH, Jimenez D, Kinne DW
Departments of Pathology, Molecular Virology and Surgery, University of Michigan, Ann Arbor, MI
Lab Invest; 46(1):50A 1982

An antigen immunologically related to mouse mammary tumor virus (MuMTV) and the major envelope glycoprotein, gp52 of MuMTV, was identified in tissue sections of human male and female mammary carcinomas using the peroxidase-antiperoxidase technique. Positive reactions with the gp52 antiserum were seen in mouse and human mammary carcinomas but not in normal mammary tissues, mammary tissues with benign diseases, and in other primary malignant neoplasms. Almost all of the 32 of 36 male mammary carcinomas were positive for the gp52-related antigen, whereas 14 of 50 of tumors from female patients were positive. The gp52-positive

tumors were significantly larger than the gp52-negative tumors in female patients. Gp52-positive tumors were also larger than gp52-negative tumors in male patients, but the difference was not statistically significant. Gp52 reactivity was also detected in metastatic mammary carcinoma in axillary lymph nodes of male and female patients. The presence of gp52-related antigen was not apparently related to tumor grade or lymphocytic infiltrate in the primary tumor. (no Refs)

20. KAPOSI'S SARCOMA - AN EMERGING EPIDEMIC.

Mansell PW
Div. Cancer Prevention, M. D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 34(2):72-74 1982

The pathobiology of Kaposi's sarcoma and the recent outbreak of the disease (greater than 200 cases) that has occurred among young male homosexuals are described. Kaposi's sarcoma may be associated with the DNA virus cytomegalovirus. It is also associated with immunosuppression and is a frequent second primary among cancer patients. The recent outbreak appears to be spreading from New York City, where 55% of the cases have originated. The population at risk (24-40 yr old) falls in age between that typical of American and European patients (60-70 yr) and that of African patients (less than 20 yr). All patients thus far examined have had anti-hepatitis B antibody or hepatitis B surface antigen, as well as anticytomegalovirus antibody titers. Cytomegalovirus has been cultured from tumor tissue in several cases. All patients in the outbreak have so far been immunosuppressed. The immunological defect appears to be progressive and long-lasting. All patients have had a history of sexually transmitted diseases, some with multiple manifestations such as hepatitis, genital herpes, gonorrhea, and condyloma. Mortality has been exceptionally high, with death occurring in a high percentage of patients within 20 mo, subsequent to unsuccessful combination chemotherapy with doxorubicin, bleomycin, Velban, and dacarbazine. Possible etiologic factors contributing to this outbreak and to malignant transformation in general are discussed. (23 Refs)

21. EVOLUTION OF INFECTIOUS MONONUCLEOSIS INTO EPSTEIN-BARR VIRUS CARRYING MONOCLONAL MALIGNANT LYMPHOMA.

Abo W, Kamada M, Motoya T, Aya T, Nakao T, Takada K, Imamura M, Iwanga M, Yano S, Osato T
(c/o Osato) Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, N15 W7, Japan
Lancet; 1(8284):1272-1276 1982

A monoclonal malignant lymphoma was diagnosed in a 30-mo-old Japanese boy, who, since the age of 12 mo, had had chronic, recurrent infectious mononucleosis manifested by repeated episodes of severe cough and high fever accompanied by marked lymphadenopathy and hepatosplenomegaly and high serum Epstein-Barr virus (EBV) antibody titers. The diagnosis of Burkitt's lymphoma was made when a cervical lymph-node biopsy specimen revealed massive proliferation of immature B-cells with starry-sky histiocytes. These lymph-node cells were characterized by a translocation between chromosomes 10 and 17. There were approx 9 EBV genome-equivalents per cell. Most cells were positive for nuclear antigen (EBNA); early antigen (EA) and viral capsid antigen (VCA) were also detected. The presence of EBV was supported by the finding that the cell-free lymph-node extract transformed cord-blood lymphocytes into EBNA-positive blast cells. The proportion of EA-positive and VCA-positive cells increased rapidly in culture for 24 hr, then the positive cells degenerated rapidly and completely. The cells also contained numerous herpes-type virus particles. The child improved considerably with cytostatic treatment and has been in remission for 2 yr. (Author abstract) (23 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

22. MONOCLONAL ANTIBODIES FROM MICE BEARING POLYOMA VIRUS-INDUCED TUMOR.

Moav N, Smorodinsky NI, Balin BA, Witz IP
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Cancer Immunol Immunother; 12(3):217-224 1982

Antibodies directed against antigens expressed on SEYF-a cells, a polyoma virus-induced sarcoma propagated in syngeneic A.BY mice, were studied and the binding characteristics of some of the resulting autologous monoclonal antibodies to various tumor cell lines and other properties of these antibodies are described. Spleen cells from SEYF-a-bearing mice 4-6 wk after transplantation were used for the hybridization experiments; 45 hybridomas were found to be positive. The antibodies produced by hybridoma F4/5.10 demonstrated high binding activity only to SEYF-a cells and very low binding to KREBS and ELD cells. Results suggested that F4/5.10 produces antibody directed against an antigenic determinant present predominantly on the SEYF-a cell membrane. Three of hybrid clones were found to produce IgG2a, three produced IgG1, and one produced IgM. The heavy chains of F4/5.10 and P3 were in the gamma-chain region, whereas the heavy chains of F7/129.7 were in the mu-chain region. When antibodies from F4/5.10 were used only SEYF-a cells (and none of the other tumor cells tested) absorbed considerable amounts of the antibodies (65%). These results, together with the results obtained from the binding experiments, strongly support the assumption that F7/129.7 antibodies are directed against a broadly distributed public determinant, while F4/5.10 antibodies are directed against a specificity that has a narrow distribution. (33 Refs)

23. ISOLATION OF TRANSFORMATION-DEFECTIVE HOST-RANGE MUTANTS OF POLYOMA VIRUS ON NORMAL MOUSE CELLS.

Feunteun J, Benjamin TL
Institut de Recherches Scientifiques sur le Cancer, BP No. 8, 94802 Villejuif Cedex, France
Virology; 119(2):310-316 1982

Host-range mutants of polyoma virus have been isolated utilizing primary mouse embryo fibroblasts as the permissive host and cells of an established 3T3 line as the nonpermissive host. Five out of five such 'mouse embryo-dependent' (MED) mutants have totally lost transforming ability. Their transformation defects can be complemented by ts-a mutants but not by hr-t mutants. Restriction enzyme digestion shows deletions of 150-200 base pairs in the proximal early region of the viral DNAs (HpaII fragment 4, 79-92 map units). None of the MED mutants produce middle or small tumor antigen species detectable by metabolic labeling and immune precipitation, and none show the middle T-antigen-associated protein kinase activity in vitro. MED mutants are thus indistinguishable from hr-t mutants previously isolated ising polyoma-transformed 3T3 cells as the permissive host. The isolation of nontransforming host-

range mutants in the absence of direct polyoma gene complementation confirms a specific prediction of the hypothesis of indirect action by the hr-t gene, according to which the inability to transform must arise concomitantly with the inability to induce a permissive state for virus growth. (Author abstract) (28 Refs)

24. SIMIAN VIRUS 40 A GENE FUNCTION: FURTHER CHARACTERIZATION AND GROWTH OF TSA TRANSFORMED CHINESE HAMSTER CELLS.

Robinson CC, Lehman JM
(c/o Lehman) Dept. Pathology, Univ. Colorado Sch. Medicine, Denver, CO, 80262
J Cell Physiol; 111(3):225-231 1982

Characterization of the tsA transformants and their growth pattern on normal cell monolayers were studied using two simian virus 40 (SV40) transformed Chinese hamster embryo cell lines, ChHA58, transformed by group A mutant ts58, and the WT virus transformed cell line, ChHWT. Characteristics used to evaluate transformation of these cells are summarized. tsA mutant transformed ChH embryo cells at 40.5 C were distributed in all phases of the cell cycle and had heavily labeled nuclei after a short 3H-thymidine label indicating that they continue DNA synthesis at the restrictive temperature for T antigen. tsA transformed cells were seeded onto monolayers of normal Chinese hamster cells. Colonies of tsA transformed cells appeared at 37 C but not at 40.5 C while no difference in colony forming ability of WT transformants was observed at these two temperatures. During these experiments no debris accumulated in the culture fluid at 40.5 C, unlike the large numbers of floating dead cells present when the tsA transformants were grown alone. Results suggested that the growing pattern of tsA mutant transformed cells at 40.5 C might be different under the two culture conditions. Viable cells were necessary to obtain growth arrest since this effect was not observed with glutaraldehyde fixed cells or conditioned medium. These experiments demonstrated that under proper substrate conditions, tsA Chinese hamster cells were arrested in DNA synthesis. (26 Refs)

25. PRESENCE IN GROWTH-ARRESTED CELLS OF CELLULAR PROTEINS THAT INTERACT WITH SIMIAN VIRUS 40 SMALL-T ANTIGEN.

Rundell K
Dept. Microbiology and Immunology, Northwestern Univ., Chicago, IL, 60611
J Virol; 42(3):1135-1137 1982

Two cellular proteins, 56K and 32K, found in association with simian virus 40 small-t antigen were not induced by viral infection. In addition, the proteins were expressed by cells in the growth arrest period, a time in which small-t function is of importance in infection and transformation. (Author abstract) (12 Refs)

26. SUSCEPTIBILITY OF BALB/CGNDU MICE TO TRANSPLANTABLE TUMORS, IN VITRO TRANSFORMED CELLS, BK AND SV40 VIRUSES, AND CHEMICAL CARCINOGENS.

Morrison DG, Moyer MP, Lynd FT, Rogers W, Moyer RC
Thorman Cancer Res. Lab., Trinity Univ., 715 Stadium Drive, San Antonio, TX, 78284
Oncology; 39(4):228-233 1982

Various oncogenic agents were employed in tumor susceptibility studies of an inbred subline of BALB/cGn mice, BALB/cGnDu, which carries a mutant gene that results in spontaneous thymic involution in homozygous recessive individuals. Of 18 transplantable tumors, 3 in vitro transformed cell lines, 2 oncogenic papovaviruses and 3 chemical carcinogens evaluated, only the Harding-Passey amelanotic melanoma produced tumors in 100% of the normal adult mice injected. The S180 pleomorphic sarcoma produced tumors in 56% of normal adult mice. Although not tumorigenic in adults, the mKSA, Morris (rat) hepatoma Number 7777, and a human papovavirus-transformed human cell induced mouse tumor line [GI110(BK) B6D2 Tu] formed tumors in 100, 62 and 70%, respectively, of recipients inoculated as neonates. SV40 and human papovavirus BK virions, as well as SV40, BK, and spontaneous in vitro transformed BALB/cGnDu cells were not tumorigenic. Although the histocompatibility antigens of these animals have not been studied, no correlations could be made between the tumor susceptibility of these animals with regard to the commonly employed inbred line BALB/c nor with regard to the range of host susceptibility of the transplantable tumors. This inbred subline represents a new strain of mice whose genetic defect makes it useful for transplantation immunology and physiological genetics. (Author abstract) (13 Refs)

27. INCREASED EXPRESSION OF SV40 T ANTIGEN AND CELL DIVISION IN SKIN FIBROBLAST CELL LINES DERIVED FROM A FAMILY AT HIGH RISK OF CARCINOMA (FAMILY G OF WARTHIN).

Lubiniecki AS, Lynch HT, Blattner WA, Guirgis H
Flow Lab., Inc., Old Springhouse Road, McLean, VA, 22102
J Cancer Res Clin Oncol; 103(2):127-133 1982

T-antigen expression in 24 of 31 skin fibroblast cell lines from members of Family G was found to be significantly elevated compared with a healthy control population. However, the pattern of elevation did not appear to be associated with cancer risk. In addition, T-antigen values were independent of the age and sex, as well as the branch of family and generation of the cell donor. Cell lines from Family G tended to divide more frequently than cell lines from control donors. This tendency was negatively associated with elevated T-antigen expression in Family-G cell lines, while control cell lines showed no such correlation. These results demonstrate that caution must be taken in evaluating potential markers of cancer risk. Superficial analysis of the data would indicate the utility of the T-antigen assay as a marker for cancer family syndrome. However, consideration of additional factors, including pedigree relationships and cell biology in vitro, indicate that SV40 T-antigen expression is an ambiguous marker of this type of cancer risk, even when large groups are studied. (Author abstract) (14 Refs)

28. MUTANT OF SIMIAN VIRUS 40 LARGE T-ANTIGEN THAT IS DEFECTIVE FOR VIRAL DNA SYNTHESIS, BUT COMPETENT FOR TRANSFORMATION OF CULTURED RAT CELLS.

Stringer JR
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
J Virol; 42(3):854-864 1982

A mutant was isolated which demonstrates that the transforming activity of simian virus 40 large T-antigen is separable from its function in viral DNA replication. The mutant, SVR9D, is nonconditionally defective for viral DNA synthesis, but competent at wild-type level for morphological transformation of cultured rat cells. The lytic growth defect in SVR9D is complemented by the simian virus 40 A gene product present

in the transformed CV1 cell line, COS1. The lesion in SVR9D DNA was mapped genetically by marker rescue of plaque formation and localized to a 214-base-pair segment of the viral genome bounded by nucleotide numbers 4100 and 4314. DNA sequence analysis showed the mutation to be an adenine-to-guanine transition at nucleotide number 4178. This change predicts a lysine-to-glutamic acid amino acid change at residue number 214 of the mutant large T-antigen polypeptide. (Author abstract) (32 Refs)

29. COVALENT AFFINITY LABELING BY PERODATE-OXIDIZED [ALPHA-32P]ATP OF THE LARGE-T PROTEINS OF POLYOMA AND SV40 VIRUSES.

Clertant P, Cuzin F
Centre de Biochimie du Centre National de la Recherche Scientifique, Universite de Nice, Parc Valrose, 06034 Nice, France
J Biol Chem; 257(11):6300-6305 1982

Incubation of crude extracts from cells lytically infected with polyoma virus in the presence of periodate-oxidized [alpha-32P]ATP led to the radioactive labeling of one mein polypeptide immunoprecipitated by anti-T antigen antibodies. It was absent from extracts of mock-infected cells and exhibited an apparent Mr value of 105,000 identical with that of the large-T viral protein. This polypeptide was unambiguously identified as large-T on the basis of the heat sensitivity of the in vitro labeling in extracts from cells infected with a tsa mutant. The amount of incorporated radioactivity was found to increase linearly with that of infected cell extract and with the incubation time. Labeling resulted from the specific binding of an oxidized ATP molecule to a nucleotide binding site of the large-T protein, since it was efficiently competed by unlabeled ATP. Study of the dependence on the concentration of oxidized ATP evidenced a first order kinetic for the labeling reaction. Similar results were obtained for the large-T protein of SV40 virus. (Author abstract) (32 Refs)

30. FUSION OF EBV TRANSFORMED B CELL LINES WITH MURINE MYELOMAS AS A VIABLE ALTERNATIVE FOR PRODUCTION OF HUMAN MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Kozbor D, Chang TH, Steplewski Z, Roder JC, Koprowski H
Department of Microbiology and Immunology, Queen's University, Kingston, Canada
Hybridoma; 1(2):200 1982

Peripheral blood B lymphocytes from donors immunized with tetanus toxoid (TT) were preselected for antigen (TT) binding cells followed by transformation with Epstein Barr virus (EBV) and cloning. A clone (B6) secreting the highest amount of monoclonal anti-TT was fused with a non-Ig secreting murine myeloma (P3x63Ag8 variant 653), selected in HAT medium containing 10-5M Oubain and cloned. Four clones selected for study were found to secrete 10-fold more monoclonal anti-TT antibody (1-2 ug/ml IgM kappa) during the six day culture period, than the parental line (B6). Human x mouse hybridoma clones required much less serum (1%) for growth and Ig production. Hybrids have been stable for 5 months and possess a full complement of murine chromosomes and a mean of 24 human chromosomes. The results show that hybridomas between EBV lines and murine myelomas offer advantages of (1) increased stablity; (2) increased antibody production; and (3) reduced serum requirement for growth in vitro. Since EBV is a known polyclonal activator, this technique suggests the possibility of expanding human B cells of rare antigen specificities prior to fusion. (1 Ref)

31. HUMAN LYMPHOMA-LYMPHOMA HYBRIDS AND LYMPHOMA-LEUKEMIA HYBRIDS. II. EPSTEIN-BARR VIRUS INDUCTION PATTERNS.

Klein G, Zeuthen J, Ber R, Ernberg I
Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden
JNCI; 68(2):197-202 1982

In addition to the spontaneous expression of markers of the early and late phases of the viral cycle [Epstein-Barr virus (EBV), early viral cycle antigens (EA), and viral capsid antigen (VCA)] by a panel of hybrid cell lines derived by fusion of human hematopoietic cell lines, the induction of these markers by three chemical inducers [5-iodo-2'-deoxyuridine, the tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA), and sodium butyrate] were analyzed. A variant of the prototype producer of lytic EBV, P3HR-1 (PICAT) was observed to show consistent low spontaneous and induced production of EA and VCA as compared to the P3HR-1 line from which it was derived. An 'autohybrid' (PICATPO-1) between these two lines showed a low production of VCA. Hybrids between Raji and P3HR-1 sublines (RUD-PICAT-1 and RUDPUT-2) showed reduced expression of EBV antigens. Both hybrids were capable of VCA expression, in contrast to the Raji parent that expressed EA but not VCA. A new Raji-Daudi hybrid (DITRUD-1) expressed spontaneous and induced EA and VCA at levels intermediate between its two parents. A different type of hybrid was derived from a Daudi subline and the K562 leukemia cell line (DUTKO-1) and was found to be capable of spontaneous as well as induced EA and VCA expression. Both DUTKO-1 and DITRUD-1 were similar to Daudi in their induction profile in respect to a very low response to TPA. (Author abstract) (20 Refs)

32. SIMILARITY OF EPSTEIN-BARR VIRUS EARLY POLYPEPTIDES INDUCED BY VARIOUS TUMOR PROMOTERS.

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Cancer Lett; 16(1):19-23 1982

The induction of Epstein-Barr virus (EBV) early antigen in EBV-harboring but nonproducing Raji cells by n-butyrate in combination with a variety of tumor promoters is reported. The overall pattern of polypeptides induced by Croton tiglium extract, Euphorbia lathyris extract, croton oil, teleocidin B, and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was strikingly similar. While the plant diterpenes (eg, TPA) differ completely in structure from teleocidin B, an indole-alkaloid, both types of compounds are tumor promoting agents and both activate EBV expression. EBV early polypeptides induced in the EBV-genome harboring Raji cells by these agents are identical. These results suggest that dissimilar tumor promoters act through a common pathway that is independent of structural considerations. (13 Refs)

33. ANALYSIS OF EPSTEIN-BARR VIRUS (EBV) OF P3HR-1: ISOLATION OF EBV WITH EBNA INDUCTION ABILITY IN HUMAN CORD LYMPHOCYTES AND WITHOUT EA INDUCTION ABILITY IN RAJI CELLS.

Yano S, Tanaka A, Takada K, Fujiwara S, Osato T, Nonoyama M
(c/o Nonoyama) Dept. Virology, Showa Univ. Res. Inst. Biomedicine Florida, 5180 113th Ave. N., Clearwater, FL, 33520
Virology; 119(2):392-398 1982

A subline of P3HR-1 cells was isolated through a prolonged (over 1 yr) propagation of the cells at a non-EBV-productive condition followed by cell cloning procedures. Cloned cells thus obtained, designated DHR1, produced EBV when brought back to the EBV-productive condition. .Restriction enzyme analysis of the viral DNA revealed that DHR1 EBV is composed of an apparently homogeneous EBV population, and it displays a similar but not identical genome organization compared with HR-1 EBV. The characteristic biological properties of DHR1 EBV included the ability to induce EBV-associated nuclear antigen (EBNA) in human cord lymphocytes and the inability to induce EBV-associated early antigen (EA) in Raji cells. These are in striking contrast to the behavior of the parental HR-1 EBV. Thus, P3HR-1 cultures after a period of nonproductivity reinitiated the production of virus with an apparently homogeneous and unique population of EBV distinguishable from the original HR-1 virus. (Author abstract) (18 Refs)

34. ANALYSIS OF DR-LIKE MOLECULES ON A MARMOSET EPSTEIN-BARR VIRUS-INDUCED CELL LINE USING A MONOMORPHIC ANTI-HUMAN HLA-DR MONOCLONAL ANTIBODY.

Teillaud JL, Charron D, Goujet-Zalc C, Mahouy G
Institut de Recherches sur les Maladies du Sang, Hopital Saint-Louis, F-75475 Paris Cedex 10, France
Eur J Immunol; 12(5):446-448 1982

Mouse anti-HLA D region-related (DR) monoclonal antibodies have been found to cross-react with peripheral blood leukocytes from one primate species, the common marmoset (Callithrix jacchus). Immunoprecipitates of radioactively labeled cells extracted from a marmoset Epstein-Barr virus-induced cell line were analyzed by one- and two-dimensional gel electrophoresis and compared with the DR antigens of a human lymphoblastoid B cell line. Two chains of estimated molecular weights of 34,000 (alpha) and 28,000 (beta), similar to the human alpha and beta chains, have been observed in marmoset immunoprecipitates. Additionally, a set of spots located in the same area as the set of invariant spots found in human HLA-DR antigens is shown by two-dimensional gel electrophoresis. Thus, cross-reacting anti-human HLA-DR monoclonal antibodies could be used to analyze the expression and the structure of marmoset DR-like antigens. (Author abstract) (19 Refs)

35. THE EARLY PATHOGENESIS OF TURKEY HERPESVIRUS INFECTION IN CHICKENS AND TURKEYS.

Fabricant J, Calnek BW, Schat KA
Dept. Avian and Aquatic Animal Medicine, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Avian Dis; 26(2):257-264 1982

T-5A and FC-126 turkey herpesviruses were inoculated into chickens and turkeys; 2-20 days later viruses were isolated from their spleens and viral internal antigen (VIA) was determined in the skin and spleen. Chickens and turkeys and the two viral isolates showed little differences in virus content of the spleen. VIA was found in the spleen of infected turkeys, but not that of infected chickens. VIA occurrence differed between strains in turkeys; no VIA was found in the thymus or bursa of either bird species. VIA was found sporadically and at low levels in the feather follicle epithelium of both species. In both chickens and turkeys, the levels of focus-forming units and VIA per 10(6) cells were similar for individual birds, and positive cells never exceeded 0.01% of the total. No statistically significant differences in relative spleen weights were found at 7, 14, or 20 days postinoculation when infected birds were compared with appropriate controls, although some spleens were judged to be enlarged at 6-7 days based on gross examination. Small foci of lymphoblastoid cells were found in the nerve plexes at 14 and 20 days in 10/12 chickens and 4/12 turkeys. The detection of turkey herpesvirus in the spleen of turkeys by immunofluorescence is the first evidence for viral replication in a lymphoid organ. (28 Refs)

36. DIFFERENT PAPILLOMAVIRUSES AS THE CAUSES OF ORAL WARTS.

Lutzner M, Kuffer R, Blanchet-Bardon C, Croissant O
Unite des Papillomavirus, Institut Pasteur, 25 rue du Docteur Roux, 75724 Paris 15, France
Arch Dermatol; 118(6):393-399 1982

We have observed four patients with oral papillomas. Two children had oral mucosal lesions characteristic of focal epithelial hyperplasia, a young man had common, wart-like lesions on his hard palate, and a male immunosuppressed renal allograft recipient had condyloma-like lesions on his gingivae. Papillomavirus-like particles were seen by electron microscopy in lesions from both patients with focal epithelial hyperplasia. No structural antigens for human papillomavirus (HPV) 1, 2, 3, or 5 were found by immunofluorescent microscopy, but further evidence of the presence of a papillomavirus was found by immunoperoxidase microscopy using a cross-reacting sodium lauryl sulfate-disrupted bovine papillomavirus 1 anti-rabbit serum sample. The distinct histologic pattern seen in focal epithelial hyperplasia suggests that a yet undescribed HPV type might be associated with this disease. Histologic, ultrastructural, and immunofluorescent microscopy and restriction endonuclease analysis all gave evidence of HPV 2 in the palatal lesions in patient 3. Evidence of papillomavirus antigen was found by immunoperoxidase microscopy in the oral condylomas from our immunosuppressed patient. (Author abstract) (31 Refs)

37. DEMONSTRATION OF PAPILLOMAVIRUS ANTIGEN IN PARAFFIN SECTIONS OF LARYNGEAL PAPILLOMAS.

Braun L, Kashima H, Eggleston J, Shah K
Dept. Pathobiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, 615 North Wolfe St., Baltimore, MD, 21205
Laryngoscope; 92(6,part1):640-643 1982

A papillomavirus antigen has been identified in tissue sections of laryngeal papillomata removed at endoscopic operations. The demonstration of the papillomavirus antigen was achieved using the peroxidase-antiperoxidase test of Sternberger after a broadly cross-reactive rabbit antiserum to the papillomavirus capsid antigen was incubated with the tissue sections. The antigen was detected in specimens from 7 of 15 patients with juvenile-onset laryngeal papillomas, but could not be demonstrated in the specimens from six patients with adult-onset papillomas. In all, 73 biopsy specimens from 21 patients

were selected for study; 18% (11/61) of the sections from the juvenile-onset patients and 0% (0/12) of the sections from the adult-onset patient specimens exhibited the papillomavirus antigen. The presence of the virus antigen did not correlate with the stage of disease, nor with the duration or severity of the illness. The implications of the findings are discussed. (Author abstract) (17 Refs)

38. FREQUENCY AND DISTRIBUTION OF PAPILLOMAVIRUS STRUCTURAL ANTIGENS IN VERRUCAE, MULTIPLE PAPILLOMAS, AND CONDYLOMATA OF THE ORAL CAVITY.

Jenson AB, Lancaster WD, Hartmann DP, Shaffer EL
Dept. Pathology, Georgetown Univ., Sch. Medicine and Dentistry, Washington, DC, 20007
Am J Pathol; 107(2):212-218 1982

Sixty-seven proliferous squamous epithelial lesions of the oral cavity were examined for the presence of human papillomavirus whole (structural) virion antigens by a peroxidase-anti-peroxidase technique having immunospecificity against genus-specific (common) antigens of the papillomaviruses. A positive reaction for papillomavirus genus specific antigens was found in 18 of 29 verrucae, 2 of 5 multiple papillomas, and 3 of 5 condylomata; common antigens were not detected in 28 keratoacanthomas. The positive reaction was invariably intranuclear in cells having a focal or diffuse distribution in the superficial epithelium. This study shows that a variety of squamous epithelial lesions of the mucosa are associated with human papillomaviruses and suggests that these viruses may play an important role in the etiology of some cases of squamous hyperplasia of the oral cavity. (Author abstract) (24 Refs)

39. SIMULTANEOUS DETERMINATION OF T-ANTIGEN AND ABO CELL SURFACE ANTIGENS IN TRANSITIONAL CELL CARCINOMA (MEETING ABSTRACT)

Kidd D, Javadpour N, Fourcroy J, O'Connel K
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The purpose of this study was to investigate the changes in cell surface antigens which result in the interruption of communication and interaction through the cell surface membrane. These changes reflect an alteration in the genome which modifies the biosynthetic pathways of the Golgi apparatus. The demonstration of T-antigen expression in breast carcinoma and the loss of blood group iso-antigens in invasive transitional cell carcinoma prompted inquiry into the correlation between the carbohydrate precursor of the human blood system MN and the epithelial surface blood group isoantigens. A red cell adherence assay to detect T-antigen on deparafinized slides of transitional cell carcinoma of the bladder was developed. Peanut agglutinin which has anti-T properties as well as other nonspecific binding sites is layered over the slides, washed, then covered with neuraminidase treated red cells. Red cell adherence was noted on areas of the bladder tumor that binds plant lectin. This was compared with the specific red cell adherence (SRCA) for ABO antigen on the same tissue samples. Of the 17 patients, 14 demonstrated loss of their cell surface ABO antigens. Of the 14, 28% demonstrated expression of the T-antigen. This would imply that T-antigens may be complementary to A, B, O, Ag in predicting potential malignancies of bladder cancer when the conventional histologic examination can not provide any prediction. (no Refs)

40. PURIFICATION OF A NATIVE MEMBRANE-ASSOCIATED ADENOVIRUS TUMOR ANTIGEN.

Persson H, Katze MG, Philipson L
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J Virol; 42(3):905-917 1982

A 15,000-dalton protein was purified from HeLa cells infected with adenovirus Type 2. Proteins solubilized from a membrane fraction of lytically infected cells was used as the starting material for purification. Subsequent purification steps involved lentil-lectin, phosphocellulose, hydroxyapatite, DEAE-cellulose, and aminohexyl-Sepharose chromatographies. A monospecific antiserum, raised against the purified protein, immunoprecipitated a 15,000-dalton protein encoded in early-region E1B (E1B/15K protein) of the adenovirus Type 2 DNA. Tryptic finger print analysis revealed that the purified protein was identical to the E1B/15K protein encoded in the transforming part of the viral genome. The antiserum immunoprecipitated the E1B/15K protein from a variety of viral transformed cell lines isolated from humans, rats, or hamsters. The E1B/15K protein was associated with the membrane fraction of both lytically and virus-transformed cell lines and could only be released by detergent treatment. Furthermore, an 11,000-to 12,000-dalton protein that could be precipitated with the anti-E1B/15K serum was recovered from membranes treated with trypsin or proteinase K, suggesting that a major part of the E1B/15K protein is protected in membrane vesicles. Translation of early viral mRNA in a cell-free system, supplemented with rough microsomes, showed that this protein was associated with the membrane fraction also in vitro. (Author abstract) (47 Refs)

41. EXPRESSION OF EUKARYOTIC VIRAL AND CELLULAR GENES.

Pettersson RF, Kaariainen L, Soderlund H, Oker-Blom N
Dept. Virology, Univ. Helsinki, Helsinki, Finland
Expression of Eukaryotic Viral and Cellular Genes. London, Academic Press, 324 pp., 1981.

Recent advances in molecular virology, molecular genetics, and recombinant DNA research are combined in a discussion of expression of eukaryotic viral and cellular genes. Structure and expression of DNA virus genes are reviewed with respect to molecular analysis of adenovirus transformation, control of adenovirus messenger (m)RNA production by differential transcription and differential stability of mRNA, an early adenovirus glycoprotein and its association with transplantation antigens, the control of adenovirus early gene expression, and mutational analysis of regulatory elements of simian virus 40. Retrovirus genes are discussed with respect to OK 10 virus-transformed bone-marrow-derived cell line, the transforming insert in the Abelson murine leukemia virus genome, and DNA intermediates in the replication of retroviruses. RNA virus genes are discussed with respect to the genome of single-stranded messenger-sense RNA viruses, influenza virus, capped cellular RNAs, drift and shift of influenza A-type virus, vesicular stomatitis virus and host cell phosphoproteins, initiation of eukaryotic protein synthesis, alphavirus gene products, Semliki Forest virus, RNA containing heterogeneous 5'-terminal nucleotide sequences, and Semliki Forest virus defective interfering RNA using DNA copies. Eukaryotic genes are discussed with respect to structure, organization and developmental expression of chorion multigene families, gene amplification and methotrexate resistance, RNA-protein complexes precipitated by Lupus antibodies, promoter sequences, expression of cloned eukaryotic genes in microorganisms, human genomic DNA-en-

coding Pro-opiomelanocortin, and functional yeast minichromosomes containing centromeric DNA. (701 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

42. ROLE OF METHYLATION IN THE INDUCED AND SPONTANEOUS EXPRESSION OF THE AVIAN ENDOGENOUS VIRUS EV-1: DNA STRUCTURE AND GENE PRODUCTS.

Conklin KF, Coffin JM, Robinson HL, Groudine M, Eisenman R
Dept. Molecular Biology and Microbiology, Tufts Univ. Sch. Medicine, Boston, MA, 02111
Mol Cell Biol; 2(6):638-652 1982

A variant chicken embryo (number 1836) cell culture was examined by immunoprecipitation and gel electrophoresis. The culture contained endogenous avian provirus ev-1 and ev-6, and spontaneously expressed the ev-1 provirus. The cells released noninfectious virions containing Rous-associated virus type O-related 70S RNA and gag gene products but devoid of reverse transcriptase activity or antigens. EV-1 encoded particles also lacked envelope glycoproteins. DNA from the spontaneously expressing 1836 cell ev-1 provirus contained deoxyribonuclease I-hypersensitive sites in both long-term repeat sequences and the 5' flanking and gag gene sequences, the DNA also contained a pattern of methylation different from that of inactive ev-1 DNA. The finding of specific sites in 1836 ev-1 DNA that are differentially methylated only in expressed ev-1 DNA suggests that a certain pattern of methylation, possibly undermethylation, effects transcriptional activation. (50 Refs)

43. POSSIBLE ROLE OF A RETROVIRUS IN THE EXPRESSION OF TUMOR-SPECIFIC ANTIGENS OF THE METH A SARCOMA.

DeLeo AB, Chang KS, Wivel NA, Appella E, Old LJ, Law LW
Sloan-Kettering Cancer Center, New York, NY
Int J Cancer; 29(6):687-693 1982

The serologically defined tumor-specific surface antigen (TSSA) of the chemically-induced BALB/c Meth A sarcoma, highly restricted to 1 of 20 sarcomas of BALB/c origin, has been detected on a Moloney murine sarcoma virus (Mo-MuSV)-transformed BALB/c3T3 cell line, designated 11A(v). The immunogenicity of the 11A(v) cell in tumor-rejection assays was specific for the Meth A sarcoma, supporting the evidence for a close relationship between the TSSA and the tumor-associated transplantation antigen (TATA) of this tumor. Infection of SC-1 cells with retroviruses present in cultured filtrates of IIA(v) cells resulted in Meth A antigen expression. The retroviruses associated with Meth A antigen expression have been tentatively identified as replication and/or transformation-defective XC-MuLV. The possible roles of Mo-MuSV and cellular genes of the BALB/c strain of mice in the expression of the Meth A antigen are discussed. (Author abstract) (43 Refs)

44. CHARACTERIZATION OF DUALTROPIC TYPE C RETROVIRUSES ISOLATED FROM SPONTANEOUS NON-T LYMPHOMAS OF SJL/J(V+) MICE.

De Rossi A, D'Andrea E, Chieco-Bianchi L
Laboratorio di Oncologia, Istituto di Anatomia Patologica, Via Gabelli 61, 35100 Padova, Italy
Tumori; 68(2):95-104 1982

Endogenous XC- viruses were isolated from non-T spontaneous lymphomas of SJL/J(v+) mice. These isolates were cloned by limiting dilution procedure and characterized for biological and immunological properties. At the electron microscope these isolates showed typical retrovirus Type C morphology. Reverse transcriptase and immunofluorescence assays showed that these viruses were infectious for mouse and heterologous cell lines. Since some of the isolates induced cytopathic foci in mink lung cultures, they had properties similar to those described for other recombinant dualtropic viruses. Using a panel of monoclonal antibodies against gp 70 and p 15 (E) viral proteins, it was observed that the dualtropic XC- viral isolates had an antigenic profile different from that of SJL ecotropic XC+ virus. (Author abstract) (37 Refs)

45. COMPARISON OF THE ENZYME-LINKED IMMUNOSORBENT ASSAY WITH AN EARLY POLYKARYOCYTOSIS INHIBITION ASSAY AND THE AGAR-GEL IMMUNODIFFUSION TEST FOR THE DETECTION OF ANTIBODIES TO BOVINE LEUKEMIA VIRUS.

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Am J Vet Res; 43(6):960-966 1982

An indirect enzyme-linked immunosorbent assay (ELISA) was developed, using as test antigen a bovine leukemia virus (BLV) glycoprotein complex (94,000 daltons). The specificity of the ELISA was determined by using specific bovine reference sera. There was a positive reaction using reference sera containing antibodies to BLV, but a negative reaction to reference sera containing antibodies to other ubiquitous bovine agents, ie, bovine viral diarrhea virus (BVDV), foamy-like syncytia virus (BSV), and bovine maedi-like (R-29) virus. The sensitivity of the ELISA for detection of antibodies to BLV was compared with that of the early polykaryocytosis inhibition assay (EPIA), which is based on inhibition of BLV-induced early syncytia formation in cell culture, and with the agar-gel immunodiffusion (AGID) test, using the major glycoprotein (gp51) as antigen. The sera that were tested came from cattle in a high occurrence leukemia herd, cattle in a commercial dairy herd, and from blood samples, obtained from cattle from various parts of Oklahoma, submitted to a diagnostic laboratory for diagnosis of BLV infection. There was 96.2% agreement in the results of all sera tested using the three serotests. The greatest number of positive sera (153) were detected by the EPIA, followed by the ELISA (148) and AGID test (148). There was disagreement in the test results of only 16 sera. Of the 200 sera tested from the commercial dairy herd, 61 (30.5%) were positive by the ELISA, 60 (30%) by the EPIA, and 57 (28.5%) by the AGID test. In the 111 sera from the diagnostic laboratory, 45 (40.5%) were positive by the ELISA, 45 (40.5%) by the EPIA, and 47 (42.3%) by the AGID test. With the 102 sera from the high occurrence leukemia herd, 42 (41.2%) were positive by the ELISA, 48 (47%) by the EPIA, and 44 (43.1%) by the AGID test. The indirect ELISA is another serotest that can be used for the diagnosis of BLV infection in cattle. It is specific, equally as sensitive as the AGID

test, rapid to perform requiring inexpensive equipment, and may be the preferred serotest for screening large numbers of animals for BLV infection. (Author abstract) (30 Refs)

46. DNA FROM CELLS INFECTED WITH RETROVIRUS D AND FROM HUMAN TUMORS - INDUCER OF THE SYNTHESIS OF NEW NONVIRION ANTIGEN.

Kosinkova NP, Pavliuchenkova RP
D. I.Ivanovskii Inst. Virology, Moscow, USSR
Vopr Virusol; (2):230-234 1982

Role of DNA of retrovirus D in the synthesis of new nonvirion antigen was studied in HEp-2 cells chronically infected with retrovirus D and in cultured cells of various human tumors. Transfection technique showed that the synthesis of new surface retrovirus D-associated antigen was induced by DNA. DNA isolated from normal human tissues failed to induce synthesis of the antigen. (22 Refs) (In RUS)

47. AMPLIFIED EXPRESSION OF MURINE LEUKEMIA VIRUS (MULV)-CODED ANTIGENS ON THYMOCYTES AND LEUKEMIA CELLS OF AKR MICE AFTER INFECTION BY DUALTROPIC (MCF) MULV.

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Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Virology; 119(2):450-464 1982

Recently, we have shown that several isolates of recombinant, dualtropic (MCF) murine leukemia virus (MuLV) can induce amplification of MuLV gag and env gene-coded antigens on thymocytes of young AKR mice and, subsequently, can accelerate leukemia in these same animals. With respect to env gene-coded antigens, it is unclear whether antigen amplification represents expression of env gene products of the input virus on the surface of infected thymocytes or whether infection by MCF viruses induces the expression other endogenous env gene sequences. Infection by antigenically marked viruses has allowed us to decide between these alternatives. We have found that AKR MCF isolates 69L1, 13, and 247 can be distinguished serologically by specific patterns of reactivity with mouse and rat monoclonal antibodies that recognize 10 distinct epitopes (single antigenic determinants) of AKR ecotropic MuLV gp70 and p15(E) proteins. Accordingly, 1-mo-old AKR mice were injected intrathymically with either MCF 69L1, MCF 13, or MCF 247 viruses and thymocytes of virus-injected mice were then assayed for amplification of specific epitopes at 32-36 days postinjection. Quantitative expression of MuLV antigens was determined by flow microfluorometry using a fluorescence-activated cell sorter. The patterns of reactivity with monoclonal antibodies which were originally determined for each virus in vitro were found to breed true on thymocytes infected in vivo. Moreover, the phenotype of virus recovered in vitro from virus accelerated leukemias was identical to that of the injected virus. Thus, the preleukemic change of MuLV antigen amplification appears to represent expression on thymocytes of env gene products encoded by the infecting MCF viral genome which continues to be expressed in the resulting leukemias without apparent changes in the recombinant env gene. (Author abstract) (36 Refs)

48. ML ANTIGEN OF DBA/2 MOUSE LEUKEMIAS: EXPRESSION OF AN ENDOGENOUS MURINE MAMMARY TUMOR VIRUS.

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Lab. Molecular Virology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Virol; 42(3):804-813 1982

Spontaneous, transplantable leukemias of DBA/2 mice express an antigen (ML) which cross-reacts with antigens of murine mammary tumor virus (MuMTV). The MuMTV cross-reactive antigen of the DBA/2 leukemias (ML cells) was found to be a glycoprotein of 78,000 mol wt containing antigenic determinants of the major MuMTV glycoprotein gp52. No MuMTV particles were produced by the ML cells, although they did contain type A particles - the pronucleocapsids of MuMTV. The ML antigen appeared to be an aberrant form of the intracellular MuMTV env precursor molecule prgp70, which was not processed properly but instead acquired extra carbohydrate groups and was expressed in uncleaved form on the cell surface. Isolation of MuMTV core protein p28 from the leukemic cells and subsequent tryptic peptide mapping analysis showed that the p28 from leukemia cells differed from the p28 of MuMTV isolated from DBA/2 mouse milk. These observations indicate that the MuMTV expressed in DBA/2 leukemic spleen cells is of a different strain than the virus secreted in lactating mammary glands of DBA/2 mice and probably represents the expression of an endogenous DBA/2 provirus. (Author abstract) (34 Refs)

49. GROWTH OF MURINE SARCOMA AND MURINE XENOTROPIC LEUKEMIA VIRUSES IN JAPANESE QUAIL: INDUCTION OF TUMORS AND DEVELOPMENT OF CONTINUOUS TUMOR CELL LINES.

Robey WG, Kuenzel WJ, Vande Woude GF, Fischinger PJ
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Cancer Res; 42(7):2523-2531 1982

The BALB/c murine endogenous xenotropic leukemia virus pseudotype of m1 Moloney sarcoma virus [m1MSV(B-MuX)] was used to productively transform diploid Japanese quail embryo cells. The majority of newly hatched quail inoculated with m1MSV(B-MuX)-transformed quail embryo fibroblast cells rapidly developed tumors which were predominantly locally invasive fibrosarcomas, but metastases were observed in two birds. In two tumor-bearing quail, lymphosarcomas were observed in conjunction with fibrosarcomas. Quail inoculated with m1MSV(B-MuX) virus or quail embryo fibroblast cells infected with helper leukemia virus did not develop tumors. A cell culture derived from one quail tumor was shown to be oncogenic in newly hatched quail. Viruses produced by m1MSV(B-MuX)-infected quail cells or quail tumors had envelope properties of BALB-derived murine xenotropic leukemia virus as measured by host range, interference, and neutralization. Virus structural antigens, proteins with mol wt of 30,000 and 70,000, were detected in tumors and tumor-derived cell lines by immunofluorescence and gel diffusion. Sera from tumored quail had high titers of type-specific BALB-derived murine xenotropic leukemia virus antibodies as determined by neutralization and immunoprecipitation. Antibodies to the putative m1 Moloney sarcoma virus V-mos gene product were not detected in sera from tumored or regressor quail. (Author abstract) (41 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

50. ANTIBODIES TO ADULT T-CELL LEUKEMIA-VIRUS-ASSOCIATED ANTIGEN (ATLA) IN SERA FROM PATIENTS WITH ATL AND CONTROLS IN JAPAN: A NATION-WIDE SERO-EPIDEMIOLOGIC STUDY.

Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, Kikuchi M, Ichimaru M, Yunoki K, Sato I, Matsuo R, Takiuchi Y, Uchino H, Hanaoka M
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Int J Cancer; 29(6):631-635 1982

A nation-wide sero-epidemiologic survey of adult T-cell leukemia virus (ATLV), detected as anti-ATLA (ATLV-associated antigen), was made in Japan. Sera from adult donors in 15 different locations were screened for anti-ATLA. High incidences (6 to 37%) of antibody-positive donors were found in seven regions, one in northern Japan, and the others in southwestern regions. These areas are ATLV-endemic areas corresponding to ATL-endemic areas. Examination of sera from healthy donors aged 6 to 80 yr in ATL-endemic areas showed an age-dependent increase of seropositive donors with a maximum of about 30% to 40 yr of age. Anti-ATLA was found in all but two of 142 patients with ATL. Anti-ATLA-positive patients with ATL were mainly found in ATLV-endemic areas and only a few in ATL-nonendemic areas. Six patients with cutaneous T-cell lymphoma in ATLV-nonendemic areas gave a negative reaction for anti-ATLA. The geometric mean titer of anti-ATLA of patients with ATL was higher than that of healthy donors. (Author abstract) (9 Refs)

51. IN VITRO STIMULATION OF RABBIT T LYMPHOCYTES BY CELLS EXPRESSING HERPES SIMPLEX ANTIGENS.

Kapoor AK, Ling NR, Nash AA, Buchan A, Wildy P
Dept. Pathology, K.G.'s Medical Coll., Lucknow, U.P., India
J Gen Virol; 59(part2):415-419 1982

Lymphocyte stimulation responses to herpes antigens were studied using virus-infected x-irradiated cells. Rabbits were immunized with herpes simplex virus Type 1 (strain HFEM) grown in RK 13 cells. For in vitro stimulation assay BHK21 cells were x-irradiated (15,000 rad) and infected with a high moi of a temperature-sensitive mutant (N102) of HFEM strain at the non-permissive temperature (38.5 C) of virus. Virus antigens were expressed on the infected cells and there was no leakage of infectious virus into the medium at 38.5 C. T lymphocytes from rabbits immunized with herpes simplex virus were specifically activated by herpesvirus-infected x-irradiated cells; lymph node cells from rabbits immunized with RK13 cells and from non-immune rabbits showed no proliferative response. (Author abstract) (15 Refs)

52. IMMUNOCOMPETENCE AND MALIGNANCY.

Melief CJ, Schwartz RS
Hematology Service, New England Medical Center Hosp., Boston, MA
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Present concepts regarding immunocompetence and malignancy are reviewed. The general applicability of the theory of immunological surveillance to the pathogenesis of cancer is questioned. Immunological surveillance arguments fail to acknowledge the parallel system of adaptive immunity - blocking antibody - which protects the tumor against the cell-mediated immunity of the host. The virulent virus strains that are used to demonstrate immunosuppression by oncogenic viruses are not considered to have any relevance to malignancies as they develop naturally. The issue of defense mechanisms against oncogenic viruses through infectious agents must be separated from that of the defense against the cells they have transformed to a malignant state. In nearly all studies designed to determine the subject's ability to respond to antigens of his own neoplasm, evidence for cell-mediated immunity against antigens of the tumor (either from the patient or from a histologically similar allogenic tumor) has been found. Two experimental models are consistent with the notion that unrestrained proliferative activity of lymphoid tissue can culminate in neoplasia: persistent antigenic stimulation combined with partial immunosuppression and chronic graft vs host reactions. Recent experimental results now permit a serious examination of the notion that the immune reaction stimulates the growth of tumors. (267 Refs)

53. IMMUNOPATHOLOGY OF LYMPHOMAS AND NATURAL KILLER CELL ACTIVITY IN WILD MICE (MUS MUSCULUS)

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Diss Abstr Int [B]; 42(8):3202-B 1982

Naturally occurring lymphomas of Lake Casitas (LC) wild mice and lymphomas induced by LC murine leukemia virus (MuLV) in NIH Swiss mice displayed remarkably similar gross, microscopic, and functional characteristics. They spared the thymus, arose primarily in the splenic red pulp, became leukemia and were comprised of stem cell lacking classical T- and B-cell markers. Cell lines were derived from 4 spontaneous lymphomas of LC mice. One of the lymphomas expressed surface Ig, Ia antigen, lacked C'3 or Fe receptors, and is a B-cell. Another line was positive for Fe receptors, non-specific esterase, phagocytosed latex beads, and is a pure culture of macrophages. The remaining 2 cell lines retained the parental null phenotype, however, the B-220 alloantigen was detected indicating an early stage of B-cell differentiation. This wild mouse lymphoma system most resembles human childhood ALL (acute lymphocytic leukemia). MuLV antigens were demonstrated by the immunoperoxidase technique in the splenic B-cell areas of viremic LC mice. Thymus cells totally lacked virus expression. Therefore, wild mouse MuLV has a specific tropism for cells of the B-lymphocyte lineage. Natural cell-mediated cytotoxicity against YAC-1 targets was measured in splenocytes from LC wild mice. Although variable levels of cytotoxicity were detected against YAC-1 normal LC spleen cells, consistently low levels of cytotoxicity against allogeneic LC lymphoma, sarcoma and carcinoma targets were found using the same splenocytes. These results indicate that LC mice possess splenocytes with the characteristics of natural killer (NK) cells as defined in inbred mice, and suggest that NK cells may not be involved in natural tumor immunosurveillance or that the development of spontaneous tumors may involve escape from NK mediated effector mechanisms. (no Refs)

54. MOLECULAR INTERACTIONS IN HUMAN T-CELL-MEDIATED CYTOTOXICITY TO EPSTEIN-BARR VIRUS. I. BLOCKING OF EFFECTOR CELL FUNCTION BY MONOCLONAL ANTIBODY OKT3.

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Cell Immunol; 69(1):113-121 1982

The ability of different anti-human T-cell lymphocyte monoclonal antibodies to inhibit the effector function of the cytotoxic T-cell response against autologous Epstein-Barr virus (EBV)-infected B-cell targets has been tested. It was found that monoclonal antibody, OKT3, which reacts with most human T cells, blocks the effector cell function in the absence of complement, an effect that was dose dependent. When monoclonal antibody OKT3 was tested at a concentration of 1 ug/ml, inhibition of cytotoxicity ranged between 50 and 80%. The F(ab')2 fragment of OKT3 inhibited as well as the intact IgG molecule, indicating that the Fc portion of the antibody is not necessary for the cytotoxicity blocking. The Fab fragment of OKT3 had lower blocking activity per microgram of protein tested. Antibodies SC1, OKT11 (anti-pan T cell), OKT8 (anti-cytotoxic/suppressor subset), and L368 (anti-HLA) did not have any discernable blocking effects. However, antibodies SC1, OKT8 and L368 could abrogate the cytotoxic activity in the presence of complement. Blocking by OKT3 was not due to its being present on the cell surface in higher concentrations than the other monoclonal antibodies since cytofluorographic analysis demonstrated that the amount of OKT8 or L368 antibodies bound on the cells was greater than OKT3. In addition, blocking was not due to antigenic modulation since incubation with antibody OKT3-F(ab')2 was not associated with a significant decrease in the amount of its reactive antigen. Under the conditions tested OKT3 did not affect cell viability or cause agglutination. (Author abstract) (34 Refs)

55. EPSTEIN-BARR VIRUS-SPECIFIC CYTOTOXIC T-CELL CLONES RESTRICTED THROUGH A SINGLE HLA ANTIGEN.

Wallace LE, Rickinson AB, Rowe M, Epstein MA
Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England
Nature; 297(5865):413-415 1982

Epstein-Barr (EB) virus-specific human cytotoxic T-cell clones, recognizing the virus-induced lymphocyte-detected membrane antigen (LYDMA) in association with one particular human leukocyte antigen (HLA)-A or -B determinant, were established in vitro. T-cells were prepared by in vitro reactivation from seropositive donor SW (HLA-A11, AW24, B7, and BW35) cells. Strong killing of the autologous cell line was not accompanied by any significant reactivity against EB virus genome-negative human leukemic cell lines HSB2 and K562, which were included as indicators of natural killer-like activity. Lysis of allogeneic EB virus-transformed cells was particularly strong when associated with either HLA-A11 or BW35 antigen matching, and progressively weaker with matching through B7 and AW24. Samples of effector cells were cloned and analyzed. Tests with clone C2 suggested specificity for the viral antigen LYDMA in association with HLA-A11. Clone C2 killed 8/8 EB virus-transformed cell lines from donors typed HLA-A11, but did not kill any of 15 corresponding lines from A11-negative donors. No lysis of EB virus genome-negative target cells was observed. Clone G13 and H8 showed similar results, while clone G9 gave a different pattern of reactivity, suggesting specific recognition of LYDMA in association with HLA-BW35. Clone G9 killed 9/10 EB virus-transformed target cell lines from donors typed HLA-BW35 but none of the 11 corresponding lines tested from BW35-negative donors or any of the relevant EB virus genome-negative target cells. The mechanisms for the observed reactivities are discussed. (24 Refs)

56. PREVENTION OF SYNGENEIC TUMOR GROWTH IN VACCINIA VIRUS-PRIMED MICE BY IMMUNIZATION WITH VACCINIA VIRUS-MODULATED TUMOR CELLS.

Wu KS, Ueda S, Sakaue Y, Ohashi Y, Ikuta K, Sugano T, Kato S
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Biken J; 24(4):153-158 1981

Immunization with vaccinia virus-infected and then x-ray-irradiated murine hepatoma MH134 cells provided C3H/He mice with strong resistance to challenge with viable MH134 cells. Male C3H/He mice of 5 to 6 wk old were primed intraperitoneally (IP) with 1 x 10(7) PFU of live vaccinia virus (Ikeda strain) after irradiation with 250 R of x-ray. Three wk after priming, the mice were immunized IP three times at weekly intervals with 1 x 10(7) x-ray-irradiated MH134 cells that had been infected with vaccinia virus 8 hr before irradiation. Over 60% of these cells showed vaccinia virus-induced antigen on their surface (membrane antigen). Challenge with viable MH134 cells was done by inoculating 1 x 10(5) cells IP 1 wk after immunization. During a 4-wk observation period, all the untreated control mice died with ascites. On the contrary, all the mice that were x-ray-irradiated, primed and immunized survived challenge with the tumor cells for at least 4 wk. The mortalities of mice in other groups that were not irradiated, or not primed, or immunized with only x-ray-irradiated tumor cells, were at lowest 50%. (Author abstract) (14 Refs)

57. ACCESSORY CELLS IN THE IN VITRO GENERATION OF TYPE C VIRUS-SPECIFIC T-KILLER LYMPHOCYTES. III. TWO METHODS OF ANTIGEN PRESENTATION TO CYTOLYTIC T-LYMPHOCYTE PRECURSORS.

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Cell Immunol; 68(2):287-301 1982

F1 hybrid mice primed in vivo with tumor cells bearing the virus-induced FMR antigen and the H-2 specificities of each parent are able to produce in vitro in secondary response cytolytic T lymphocytes (CTL) reacting with FMR in the context of the H-2 antigens of both parents. This suggests that the processing in vivo of the immunizing cells by F1 macrophages results in the presentation of FMR antigens in the context of both H-2 specificities. It has also been suggested that FMR antigens are recognized by cytolytic T-lymphocyte precursors (CTL-P) at the surface of tumor cells and not of macrophages. The results reported here show that there are two methods of CTL-P priming: (a) in most cases, FMR antigens are presented directly by the tumor cells; (b) however, in the absence of antigen-presenting tumor cells in vivo or in vitro, macrophages present FMR to CTL-P. The presentation by macrophages appears less efficient but is probably sufficient to explain the priming of memory cells corresponding to both parental H-2. (Author abstract) (17 Refs)

58. SHUT-DOWN OF VIRUS SYNTHESIS DURING PROGRESSION OF ERYTHROLEUKEMIA INDUCED BY FRIEND VIRUS IN MICE.

Yoosook C
Dept. Microbiology, Faculty Science, Mahidol Univ., Rama 6 Road, Bangkok 4, Thailand
Int J Cancer; 29(6):659-665 1982

Infection of (C57BL/6 x DBA/2)F1 (BDF1) mice with 2,500 FFU of Friend virus complex (FV) resulted in erythroleukemia followed by recovery, at which time virus could not be detected in the spleens of mice, and with splenomegaly (progressor mice) or without splenomegaly (regressor mice). Progressor and regressor mice developed equally high amounts of FV-neutralizing activity in their sera. Progressor mice contained cells capable of producing virus, despite the lack of viral envelope antigen(s) in their spleens. The tropism of FV recoverable from the spleens of secondary recipients, injected with spleen cells from progressor mice, did not show any change, although the viral genome was present in Fv-1-restrictive host for at least 7 wk. When the number of spleen colony-generating cells was enumerated, by the spleen colony assay, the frequency in normal syngeneic and in allogeneic hosts was approx the same at the early stage of erythroleukemia but was about 1,000 times higher in the syngeneic recipients during leukemia progression. These spleen colony-generating cells were considered to be FV-transformed cells capable of self-renewal and capable of generating infectious centers (IC), respectively. Most of these transformed cells might be non-producer leukemia cells. (Author abstract) (28 Refs)

59. INTERFERON INCREASES HLA SYNTHESIS IN MELANOMA CELLS: INTERFERON-RESISTANT AND -SENSITIVE CELL LINES.

Basham TY, Bourgeade MF, Creasey AA, Merigan TC
Div. Infectious Diseases, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(10,part1):3265-3269 1982

We report that human leukocyte interferon preparations increase the expression of beta2-microglobulin by 100-200% on the surface of normal fibroblast and melanoma cell lines sensitive to interferon. This increase in expression can be correlated with an increase in HLA synthesis as measured by incorporation of [35S]methionine in these antigens. This enhanced HLA synthesis, which is 5-to 17-fold, is time dependent and dose related. Synchronized cells in the G0/G1 phase of the cell cycle appear to be more sensitive to this interferon action. Neither an increase in surface expression nor in HLA synthesis is observed in a melanoma cell line resistant to the antiviral and antigrowth effects of interferon. Furthermore, there appears to be a stronger correlation between this increased HLA synthesis and the antiviral function that between it and the antiproliferative action of interferon. (Author abstract) (18 Refs)

60. THE ANTITUMOR AND ANTIVIRAL EFFECTS OF POLYCARBOXYLIC ACID POLYMERS.

Ottenbrite RM
Dept. Chemistry, Virginia Commonwealth Univ., Richmond, VA, 23284
ACS Symp Ser; 186:205-220 1982

Polycarboxylic acid polymers (PAP) are reviewed in relation to: antitumor and antiviral activity, toxicological effects, macrophage activation by PAP immunopotentiators, and clinical effects. Structure and mol wt (MW) of PAP play an important role in relation to biological activity. In studies with maleic anhydride copolymers and 2,3-dicarboxynorborn-5-ene copolymers, little activity was observed for the 10,000-30,000 MW fraction while the lower MW fractions (1,000-10,000) all produced good activity, in many cases better than pyran. The toxicity of PAP is more sensitive to polymer structure and MW than antitumor activity. Polyanion polymers sensitize mice to bacterial endotoxin; this action is strikingly dependent on MW. Synthetic polyanionic immunopotentiators such as pyran and polyacrylic acid are potent activators of macrophages. Recent studies indicate that macrophages which were activated by pyran increase biochemical activity, are cytotoxic for tumors, and have a new macrophage cell surface antigen (AMphiSCA). (60 Refs)

OTHER RELATED STUDIES

61. DETECTION OF CIRCULATING TUMOUR-ASSOCIATED ANTIGENS IN SERUM OF WOMEN WITH CERVICAL NEOPLASIA. USE OF RABBIT ANTISERUM TO A CONTINUOUS CANCER CELL LINE (C-4111).

Adelusi B, Nahmias AJ, Ibrahim AN, Auersperg N
Dept. Obstetrics and Gynecology, Univ. Ibadan, Coll. Medicine, Ibadan, Nigeria
Br J Obstet Gynaecol; 89(3):238-240 1982

Hyperimmune rabbit sera to partially purified human cervical cancer tissue antigen (CaCxTAA) and to human cervical cancer culture cell line antigens (C-4II-TAA) were used to demonstrate circulating tumor-associated antigens (C-TAA) in the sera of women with cervical neoplasia. Rabbit anti-CaCx serum detected C-TAA in 80% of the 60 sera from women with invasive cancer, cancer in situ and severe dysplasia and the rabbit anti-C-4II serum detected 67% of these cases. Negative reactions were obtained in over 95% of the 154 control sera with either rabbit serum. These results suggest that, in view of the difficulty of obtaining large specimens of cervical cancer tissues for the development of immunodiagnostic procedures, the use of a cervical cancer cell line, such as C-4II, appears desirable. Such cell lines would also be advantageous for studies aimed at providing further support for the association between genital herpes simplex virus infection and human cervical cancer. (Author abstract) (10 Refs)

62. DIFFERENT EXPRESSION OF LYT DIFFERENTIATION ANTIGENS AND CELL SURFACE GLYCOPROTEINS BY A MURINE T LYMPHOMA LINE AND ITS HIGHLY METASTATIC VARIANT.

Altevogt P, Kurnick JT, Kimura AK, Bosslet K, Schirrmacher V
Institut fur Immunologie und Genetik, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Eur J Immunol; 12(4):300-307 1982

Cloned lines of the methylcholanthrene-induced DBA/2 T lymphoma Eb and its highly metastatic variant line ESb were analyzed for differences in the expression of serologically detectable cell surface differentiation markers. Flow cytofluorographic analysis of cells stained with fluorescein isothiocyanate-conjugated monoclonal rat anti-mouse Thy-1, Lyt-1, Lyt-2 and complement-dependent cytotoxicity with mouse alloantisera against Lyt-3.2 and Ly-6.2 revealed, for the parental low metastasizing line, Eb, a phenotype of Thy-1+, Lyt-1-, Lyt-3+, Ly-6+, whereas the highly metastasizing variant line typed as Thy-1-, Lyt-1+, Lyt-2-, Lyt-3-, Lyt-6-. Analysis of

galactose oxidase/NaB3H4-labeled glycoproteins from Eb and ESb clones by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate showed further phenotypic differences. Selective binding of radiolabeled glycoproteins to Helix pomatia or Vicia villosa-Sepharose, respectively, allowed the identification of T130 to be expressed on Eb cells and T145 to be expressed on some ESb clones. The latter antigen is expressed on murine cytotoxic T lymphocytes. Immune precipitation analysis revealed that Eb and ESb bear different molecular forms of the T200 antigen. Comparisons of iodinated surface proteins derived from tumor cells either treated or untreated with tunicamycin indicated that many of the differences in membrane proteins between Eb and ESb cells could be attributed to differences in glycosylation. Our results, derived from a defined tumor system of lymphoid origin, show that the progression from a low to a high malignant tumor line can be associated with changes in the expression of various defined cell surface differentiation antigens. The question of a possible relationship between tumor progression and cell differentiation or dedifferentiation is discussed. (Author abstract) (47 Refs)

63. IDENTIFICATION OF AN ANTIGEN ASSOCIATED WITH TRANSFORMING GENES OF HUMAN AND MOUSE MAMMARY CARCINOMAS.

Becker D, Lane MA, Cooper GM
(c/o Cooper), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Proc Natl Acad Sci USA; 79(10,part1):3315-3319 1982

Sera from tumor-bearing mice immunoprecipitated an 86,000-dalton glycoprotein from extracts of NIH cells transformed by human mammary carcinoma DNA. This antigen was not immunoprecipitated from extracts of NIH 3T3 cells, spontaneously transformed NIH cells, NIH cells transformed by normal human DNA, NIH cells transformed by human bladder carcinoma DNA, or NIH cells transformed by Rous sarcoma virus DNA. In addition, sera from mice bearing tumors induced by NIH cells transformed by either normal human DNA or human bladder carcinoma DNA did not immunoprecipitate this antigen from extracts of NIH cells transformed by human mammary carcinoma DNA. However, this antigen was immunoprecipitated by sera from mice bearing tumors induced by NIH cells transformed by mouse mammary carcinoma DNAs and from mice bearing primary mammary carcinomas. These results indicate that this glycoprotein represents an antigen that is specifically associated with expression of the transmissible transforming genes of human and mouse mammary carcinomas. (Author abstract) (15 Refs)

64. DETECTION OF TUMOR ANTIGENS BY SYNGENEIC ANTISERUM ON IN VITRO-TRANSFORMED TRACHEAL EPITHELIAL CELL LINE 2-10-1.

Braslawsky GR, Kennel SJ, Steele V, Nettesheim P
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Int J Cancer; 29(6):677-681 1982

Sera obtained from rats showing transplantation immunity to syngeneic, malignant epithelial cell line, 2-10-1, were used to identify antigens associated with transformation in vitro. The 2-10-1 cell line was derived from exposure of tracheal explants, in vitro, to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Tumorigenic passages of the cell line were shown to have common antigenic determinants, shared by independently transformed malignant tracheal epithelial cell lines, as well as antigenic determinants that appear to be limited to the immunizing cell line, 2-10-1. Care was taken to ensure that antibodies were not produced against viral antigens or non-specifically absorbed serum components. Early passages of the 2-10-1 cell line were not tumorigenic in athymic BALB/c (nu/nu) mice, but became malignant with serial passage in vitro. Antigenic specificities recognized by 2-10-1 immune sera were also present on early-passage 2-10-1 cells that had not as yet acquired the malignant phenotype. Such antigen expression must be an early event in neoplastic development. (Author abstract) (20 Refs)

65. CHARACTERISTICS OF HODGKIN'S DISEASE-DERIVED CELL LINES.

Diehl V, Kirchner HH, Burrichter H, Stein H, Fonatsch C, Gerdes J, Schaadt M, Heit W, Uchanska-Ziegler B, Ziegler A, Heintz F, Sueno K
Hamatologie/Onkologie, Medizinische Hochschule, Karl-Wiechert-Allee 6, 3000 Hannover, W. Germany
Cancer Treat Rep; 66(4):615-632 1982

In the last 3 yr we were able to establish five long-term in vitro cell cultures from biopsy specimens taken preterminally from four patients with histologically proven Hodgkin's disease (nodular sclerosing type, clinical Stage IVB). Four of the lines are continuously proliferating in vitro; one culture stopped growth for unknown reasons after 7 months. When culture conditions were modulated, the first culture, L 428, gave rise to two sublines: L 428 KS, after adaptation to calf serum, and L 428 KSA, permanently growing as an adherent monolayer line after treatment with a phorbol ester (12-O-tetradecanoylphorbol-13-acetate) for 3 wk. Cell-marker analysis by conventional means (SIg, cIg, rosette formation, Epstein-Barr virus reactivity, cytochemistry, phagocytosis, and lysozyme production) and with monoclonal antibodies directed against various human lymphoid, myeloid, and monocytoid antigens showed that the tested cell lines are clearly different from all hitherto described hematopoietic lines; they most likely represent a cell type resembling an early myeloid-monocytoid progenitor cell. Conditioned medium of the L 428 cells and its two sublines showed colony-stimulating factor activity and suppression of spontaneous cell-mediated cytolysis of L 428 KS and K 562 cells. (Author abstract) (26 Refs)

66. ASSOCIATION BETWEEN HLA ANTIGENS AND HEPATOCELLULR CARCINOMA (MEETING ABSTRACT)

Karvountzis GJ, Stavropoulou C, Hadziyannis SJ, Pathouli C, Renieri N, Komninos Z
Second Department of Medicine, Athens University and National Histocompatibility Center, Athens, Greece
Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Though genetic factors may play a role in the development of hepatocellular carcinoma (HCC), studies on genetic predisposition for HCC linked to the HLA antigens are rare and the results negative or controversial. In this study HLA types of 45 patients with HCC coming from a Caucasian ethnic group with a high HCC prevalence were investigated and the results were compared to those of 200 unrelated healthy controls. All patients with HCC had a firm diagnosis confirmed histologically. HBsAg and alpha1-fetoprotein (alphafp) were tested in all patients by RIA (radioimmunoassay). For HLA typing the microlymphocytotoxicity Terasaki's technique was used. One hundred antisera were used in each case for the detection of 11 HLA-A and 19 HLA-B specificities. Apparent distribution differences between patients and controls were restricted to HLA-A3, HLA-B7 and HLA-B14. These differences were sta-

tistically significant only for B7 and B14 and B14. The observed increases of A3 reached statistical significance in the group of HBsAg positive patients. The above association between particular HLA antigens (A3, B7, B14) and HCC observed in a Caucasian ethnic group, is in contrast to the negative results reported in South African Blacks and suggests that in the population studied genetic factors linked to HLA antigens are of importance in the development of HCC. (no Refs)

67. IMMUNOGENIC VARIANTS OBTAINED BY MUTAGENESIS OF MOUSE MASTOCYTOMA P815: IV. ANALYSIS OF VARIENT-SPECIFIC ANTIGENS BY SELECTION OF ANTIGEN-LOSS VARIANTS WITH CYTOLYTIC T CELL CLONES.

Maryanski JL, Boon T
Ludwig Inst. Cancer Res., UCL 74.59, 74 Ave. Hippocrate, B-1200 Brussels, Belgium
Eur J Immunol; 12(5):406-412 1982

Mouse mastocytoma P815 tumor cell variants that express new individual antigens were subjected to immunoselection in vitro with specific cytolytic T lymphocyte (CTL) clones. From one variant (P35) a number of resistant clones were isolated after a single-step selection. These immunoselected clones (P35 iscA-) proved to have acquired a stable and complete resistance to lysis by the selecting CTL, but remained sensitive to lysis by a CTL clone that recognizes a common P815 antigen. However, when these P35 iscA- clones were used to stimulate in vitro spleen cells from mice immunized with variant P35, the cytolytic activity was significantly higher on P35 and P35 iscA- targets than on the original P815 clone (P1). This indicated that P35 iscA- cells, which had lost a P35-specific determinant (P35A), had nevertheless retained another P35-specific determinant (P35B). CTL clones directed against the residual P35B determinant were then isolated. When P35 cells were submitted to selection with anti-P35B CTL, resistant clones (P35 iscB-) were obtained that were still lysed by anti-P35A and anti-P815 CTL clones. Tum- variant P35 therefore carries at least two specific determinants that can be lost independently. These results show the possibility of using selection with CTL clones to separate different components of complex cell surface antigens. The correlation between antigen expression and tumorigenicity was also examined. Antigen-loss P35 iscA- clones were found to be more tumorigenic than variant P35 which has a greatly reduced tumorigenic capacity compared to the original P815 tumor. This correlation suggests that the P35 determinant that was no longer expressed by the P35 iscA- clones is recognized on the original P35 tum- variant as a tumor rejection antigen. (Author abstract) (21 Refs)

68. EPIDEMIOLOGY OF NON-A NON-B TYPE HEPATITIS - FOCUS ON RESULTS OF STUDYING REGIONAL PREVALENCES.

Matsushita K, Toyokawa H. Terashima A, Ohori K
Hamamatsu Medical Coll., Hamamatsu, Japan
Nippon Rinsho; 40(1):247-255 1982

Prevalence of hepatitis in two wards of Jyosui-City was compared with that in other wards. Analysis of incidence was performed with respect to regional and temporal factors, sex, age-grouping, family history, rates of positive findings of hepatitis B serum (HBs) antigen, HBs antibody, or hepatitis B complement antibody, and types of drinking water consumed. (10 Refs) (In JPN)

69. RELATIONSHIP BETWEEN THE REARRANGEMENT OF IMMUNOGLOBULIN GENES, THE APPEARANCE OF A B LYMPHOCYTE ANTIGEN, AND IMMUNOGLOBULIN SYNTHESIS IN MURINE PRE-B CELL LINES.

Sugiyama H, Akira S, Yoshida N, Kishimoto S, Yamamura Y, Kincade P, Honjo T, Kishimoto T
Third Dept. Internal Medicine, Osaka Univ. Medical Sch., Fukushima-ku, Osaka, Japan
J Immunol; 128(6):2793-2797 1982

Eighteen Abelson virus-transformed immature B cell lines were established and immunoglobulin biosynthesis, expression of a B lymphocyte antigen detected by a monoclonal antibody, and rearrangement of immunoglobulin genes in these cell lines were studied. Only one cell line (A1) synthesized mu-chains but no light chains, and the other cell lines synthesized no detectable immunoglobulins. None of the cell lines established had detectable membrane-associated IgM. Fifteen cell lines expressed a B lymphocyte antigen on their cell surfaces. In three cell lines, however, the majority (greater than 99%) of cells did not express this antigen. Heavy chain genes were rearranged on both chromosomes in all the cell lines, although one heavy chain gene was deleted in three cell lines. In 12 of 18 cell lines, one or both kappa-chain genes were rearranged. In six cell lines, however, both kappa-chain genes remained in embryonic form; lambda-chain genes were in embryonic form in all the cell lines. These results suggested the hierarchy of Ig gene rearrangements, beginning with mu and proceeding to kappa and then to lambda. JH rearrangement was also shown to precede the appearance of a B lymphocyte antigen. In three cell lines (A1-A3), which were considered subclones derived from a single common precursor, it was suggested that one rearranged JH gene was functional, and the other was nonfunctional, indicating that allelic exclusion already operated in pre-B cells. (Author abstract) (23 Refs)

70. DIFFERENTIATED AND UNDIFFERENTIATED CHARACTERISTICS OF ONCOGENIC TROPHOBLAST CELL LINES DERIVED FROM MURINE PLACENTAS (MEETING ABSTRACT)

Tanaka K, Chang KS
No affiliation given, Log, T.
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

By in vitro cultivation of placentas of various mouse strains, we established trophoblast cell lines. These cell lines exhibit characteristics which are considered to be differentiated in some and undifferentiated in other aspects, as exemplified by cells of teratoma and embryonal carcinoma, respectively. Production of gonadotropin-like substance and estradiol, production of beta2-microglobulin, susceptibility to infection by polyoma virus (but not SV40 or type C retroviruses), and ability to produce interferon after stimulation with Sendai virus are characteristics associated with differentiation. Lack of detectable H-2 antigen, Fc receptor sites, Thy 1 antigen, and surface immunoglobulin determinants, lack of susceptibility to the action of murine interferon are characteristics associated with the undifferentiated state of these trophoblast cells. The resistance to type C retrovirus infection is due to a block of viral replication after the stage of viral adsorption and penetration because type C retrovirus pseudotypes of vesicular stomatitis virus, VSV(MuLV), can infect these cell to produce VSV progeny and cytopathic effects. The trophoblast cell lines in-

duced carcinomas after injection into adult mice of original host strains. Transplantation of the trophoblast tumor cells to various allogeneic mouse strains revealed that some strains accepted the transplant and some strains rejected. The lack of H-2 antigen expression is an important factor in their transplantability across histocompatibility barriers. The lack of H-2 antigen in trophoblast cells of placenta may contribute to the retention of the conceptus by the maternal uterus, guarding off the maternal transplantation-rejection immune reactions. The role of interferon at this site has not been elucidated. However, our experiments revealed that trophoblast cells are sensitive to natural killer (NK) cells and that this sensitivity is significantly reduced by pretreatment of these cells with murine interferon. Therefore, although trophoblast cells are not sensitive to interferon action in terms of protection against VSV infection, they are nevertheless sensitive to the protective action of interferon against the cytotoxic effect of NK cells. (1 Ref)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. HEPATITIS B VIRUS AND PRIMARY HEPATOCELLULAR CARCINOMA: FAMILY STUDIES IN KOREA.

Hann HW, Kim CY, London WT, Whitford P, Blumberg BS
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Int J Cancer; 30(1):47-51 1982

Chronic infection with hepatitis B virus (HBV) is closely associated with the etio-pathogenesis of primary hepatocellular carcinoma (PHC). It has been proposed that infection with HBV early in life, frequently transmitted by an HBV-carrier mother, leads to persistent infection with HBV, which in turn is associated with the development of chronic active hepatitis (CAH), post-necrotic cirrhosis and PHC. If this view is correct, then there should be clustering of chronic carriers of HBV in families of patients with chronic liver disease. We tested this hypothesis in Korea by collecting serum from 132 patients with these chronic liver diseases admitted to the Seoul National University Hospital and 664 of their first-degree relatives. Sera were assayed for hepatitis B surface antigen

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(HBsAg), antibody to HBsAg (anti-HBs) and antibody to hepatitis B core antigen (anti-HBc). Almost all cases showed evidence of present or past infection with HBV. Mothers of patients were more frequently HBsAg(+) than age-matched women in the control population or wives of patients. Five of 23 fathers were also HBsAg(+) compared with 1 of 25 age-matched controls. There was a deficit of anti-HBs in the fathers of cases compared with the controls. Siblings of patients were frequently HBsAg(+), with the highest prevalence in brothers. Family history shows that five fathers, two mothers and five brothers of cases have died of PHC. These data are compatible with the hypothesis tested and lend further support to the view that prevention of infection with HBV will lead to a marked decrease in the incidence of CAH, cirrhosis and PHC in areas where these diseases are endemic. Members of the families of patients with these diseases are at high risk of developing persistent infection with HBV and chronic liver disease. It would be appropriate to focus preventive strategies on infants and children in such families. (19 Refs)

2. RESISTANCE TO IRON ACCUMULATION AND PRESENCE OF HEPATITIS B SURFACE ANTIGEN IN PRENEOPLASTIC AND NEOPLASTIC LESIONS IN HUMAN HEMOCHROMATOTIC LIVERS.

Hirota N, Hamazaki M, Williams GM
American Health Foundation, 1 Dana Road, Valhalla, NY
Hepatogastroenterology; 29(2):49-51 1982

Two human cases of hepatocellular carcinoma combined with primary hemochromatosis and liver cirrhosis were studied with special reference to liver lesions displaying resistance to iron accumulation, and presence of hepatitis B surface antigen. Hepatocellular carcinomas, as well as small island of hepatocytes within regenerative nodules, were free of the iron accumulation which otherwise occurred throughout the remainder of the hemochromatotic liver parenchyma. A positive reaction for hepatitis B surface antigen using the orcein staining method occurred randomly in iron-containing hepatocytes and in clusters of iron-deficient hepatocytes in cirrhotic nodules, but completely iron-free cells of foci and carcinomas were negative for orcein. Therefore, these iron-free foci are suggested to be precursors to the carcinoma. (Author abstract) (14 Refs)

3. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR-ASSOCIATED ANTIGENS.

Starling JJ, Sieg SM, Beckett ML, Schellhammer PF, Ladaga LE, Wright GL
Dept. Biochemistry, Eastern Virginia Medical Sch., Norfolk, VA, 23501
Cancer Res; 42(8):3084-3089 1982

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of P3X63/Ag8 mouse myeloma cells with spleen cells from BALB/c mice immunized against the prostate cancer cell line DU145. The hybrids were screened for antibody production using glutaraldehyde-fixed cells in a solid-phase radioimmunoassay. Antibody-binding specificity was also checked by quantitative adsorption, membrane immunofluorescence, and complement-dependent cytotoxicity assays. A hybridoma clone (83.21) was isolated that secreted antibodies which preferentially bound to several prostate and bladder cancer cell lines but did not bind to a variety of other normal and malignant human cell lines. This antibody also reacted with a cytomegalovirus-transformed human embryonic lung cell line but not to normal human embryonic lung cells. Quantitative adsorption studies demonstrated that the 83.21 monoclonal antibody was strongly reactive to membrane preparations from human prostate adenocarcinoma tissue and a liver metastasis of prostate carcinoma. Little or no binding activity was observed against two other prostate carcinomas, benign prostatic hyperplasia, normal prostate, or normal liver. Binding studies indicate that the 83.21 monoclonal antibody does not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, human leukocyte antigen, Beta2-microglobulin, HLA-Dr antigens, fibronectin, or prostate antigen. The data indicate that we have isolated a monoclonal antibody that binds to an antigen(s) expressed by several urogenital carcinoma cell lines as well as human prostate tumor tissue and that the antibody is not directed against well-known human tumor cell markers. (Author abstract) (37 Refs)

4. SERA FROM BREAST CANCER PATIENTS CONTAIN AN IGA ANTIBODY TO A BREAST CYST FLUID COMPONENT.

Witkin SS, Richards JM, Bongiovanni AM, Breed CN, Day NK
Dept. Obstetrics and Gynecology, Cornell Univ. Medical Coll., New York, NY, 10021
Clin Immunol Immunopathol; 23(2):358-365 1982

We have previously demonstrated that aspirated breast cyst fluids from women with benign breast disease contained a particulate component (BCF-PC) that reacted with antiserum to the murine mammary tumor virus (MuMTV). Since women with breast cancer contain antibodies and antigens reactive with MuMTV it was of interest to measure the immune response in breast cancer patients to the BCF-PC. Sera were obtained from breast cancer patients prior to surgery and 5 days postmastectomy, from women with benign breast disease and from healthy women. Analysis for antibody to the BCF-PC was by an enzyme-linked immunosorbent assay. IgA from premastectomy breast cancer patients was significantly more reactive with the BCF-PC than was IgA from women in the other categories (p less than 0.001). In contrast, IgG binding to the BCF-PC did not differ among the various groups. It was further demonstrated that the reactivity of IgA from any particular serum for the BCF-PC remained constant for different BCF-PC isolates. Other fractions of breast cyst fluids were unreactive with IgA from breast cancer patients. Determination of serum IgA levels in these women revealed that the mean IgA level was significantly higher in healthy women than in the other categories (p less than 0.001). Individual IgA levels and levels of IgA antibody to the BCF-PC were found to be not correlated in breast cancer patients. These results indicate that the production of a specific IgA antibody to the BCF-PC increases in sera of patients with breast cancer. Lastly, it was shown that preincubation of patients' sera with disrupted MuMTV, but not intact MuMTV, severely reduced subsequent IgA binding to the BCF-PC. The analysis of sera for IgA antibody to the BCF-PC may be of value for the detection of breast cancer or its recurrence. (Author abstract) (20 Refs)

5. BURKITT'S LYMPHOMA.

Ziegler JL
Veterans Admin. Medical Center, San Francisco, CA
CA; 32(3):144-161 1982

Etiology, clinical features, staging, treatment, and immunology of Burkitt's lymphoma are reviewed. Most, but not all cases are associated with Epstein-Barr virus (EBV); the causative role of EBV, if it exists, may be related to differences in viral strains. In addition to EBV, genetic factors, immunoregulatory determinants related to environment, and possibly an RNA virus have also been suggested as causes. Systemic che-

motherapy is the treatment of choice. After complete remissions lasting about 1 yr, recurrence is rare. Prognosis is directly related to the tumor burden upon initial presentation. Burkitt's lymphoma is one of a dozen neoplasms that can be cured by drugs alone. It is the most likely candidate for a virus-induced human tumor. Studies of the association of Burkitt's lymphoma and EBV led to the discovery of EBV as the cause of infectious mononucleosis. Experimental and clinical studies of Burkitt's lymphoma have led to important advances in immunobiology and tumor immunology. Promising approaches in immunotherapy include rapid removal of antigen excess and immune complexes from the circulation and enhancement of normal immunoregulatory controls of the body. (121 Refs)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

6. HLA-DR TYPING OF FETAL HUMAN SPLEEN AND LIVER LYMPHOBLASTOID CELLS TRANSFORMED BY EPSTEIN-BARR VIRUS.

Mandel TE, Jack I, Tait BD

Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia

Transplantation; 34(1):50-53 1982

Because few HLA-DR-positive cells are present in the spleen and liver, full HLA typing cannot be performed. However, B lymphocyte precursors can be transformed with Epstein-Barr virus to produce lymphoblastoid cells which express HLA-A, B, and DR antigens. Successful transformation was achieved, usually with spleen and liver, in nine fetuses aged from 15 to 18 wk, mostly within 7 to 14 days of initiation of the cultures. Spleen-derived lymphoblasts were more suitable for typing because of their greater homogeneity and higher viability. Tissues from two 13-week fetuses from prostaglandin-induced abortions and from a spontaneously aborted 22-week fetus could not be transformed. This is probably attributable to prolonged ischemia before the tissues were obtained but, in the 13-week fetuses, absence of B lymphocyte precursors was not excluded. HLA-DR typing may be useful in obtaining well matched donor-recipient pairs in fetal pancreatic islet transplantation. (Author abstract) (33 Refs)

7. SOLID-PHASE RADIOIMMUNOASSAYS FOR EPSTEIN-BARR VIRUS-ASSOCIATED ANTIGENS.

Dolken G, Gier A, Finke J, Weltzmann U

Abt. Hamatologie und Onkologie, Medizinische Universitatsklinik, Hugstetter Strasse 50, D-7800 Freiburg, W. Germany

Ric Clin Lab; 12(1):307-312 1982

Epstein-Barr virus (EBV)-associated antigens EA (early antigen), MA (membrane antigen) and VCA (viral capsid antigen) have been detected and defined by the reaction of human sera with selected targets cells. Solid-phase radioimmunoassays for the EBV-associated nuclear antigen (EBNA), EA, VCA and MA have been established by use of antigen containing cell extracts immobilized in polyacrylamide gel and 125I-labeled IgG prepared from anti-EBV positive and negative sera. Methods are given for the preparation of specific reagents for these antigens. (9 Refs)

8. INTERACTION OF EPSTEIN-BARR VIRUS WITH LEUKAEMIC B CELLS IN VITRO. II. CELL LINE ESTABLISHMENT FROM PROLYMPHOCYTIC LEUKAEMIA AND FROM WALDENSTROM'S MACROGLOBULINAEMIA.

Finerty S, Rickinson AB, Epstein MA, Platts-Mills TA

Dept. Pathology, Medical Sch., Univ. Bristol, Bristol, England

Int J Cancer; 30(1):1-7 1982

Leukemic B-cell populations were prepared from six patients with high-count prolymphocytic leukemia (PLL) as well as from one patient with Waldenstrom's macroglobulinemia (WM) in frankly leukemic phase, and their response to in vitro Epstein-Barr (EB) virus infection was monitored in terms of expression of the virus-associated nuclear antigen EBNA and of virus-induced transformation to continuous cell lines. The individual leukemic populations, tested on several occasions, gave reproducibly different responses one from another which were not obviously related to differences either of surface immunoglobulin phenotype or of immunoglobulin secretor status in vivo. After infection, four out of six PLL populations showed either transient or a more persistent expression of EBNA, always involving a minority of the cells, with no evidence of any virus-induced transformation up to 6 wk. In contrast, two out of six PLL samples as well as the WM sample rapidly gave rise to EBNA-positive cell lines which, on the evidence both of restricted immunoglobulin class expression and of abnormal marker chromosomes, were clearly derived from the leukemic cells. Further comparative studies of such leukemic B-cell populations may help to define host cell components necessary for the triggering of EB-virus-induced cellular transformation. (Author abstract) (32 Refs)

9. EPSTEIN-BARR VIRUS ANTIGENS -- A CHALLENGE TO MODERN BIOCHEMISTRY.

Thorley-Lawson DA, Edson CM, Gellinger K

Dept. Medicine, Div. Geographic Medicine, Tufts Univ. Medical Sch., Boston, MA, 02111

Adv Cancer Res; 36:295-348 1982

The serologically defined antigens of Epstein-Barr virus (EBV) are reviewed, including transformation antigens, early antigens, and late antigens. EBV nuclear antigens; lymphocyte-determined membrane antigens; intracellular early antigens and early membrane antigens; late membrane antigens and viral capsid antigens; the molecular biology of antigens and the polypeptides; and immune responses to viral antigens are discussed. Of the 50 or more polypeptides that could theoretically be coded by the 85-90 x 10(6) mol wt of unique DNA in EBV, 20-25 polypeptides are known. Defining the specificity and function of EBV for various antigens will require use of a permissive in vitro system. Since this has not been discovered, the use of monoclonal reagents seems to be the most promising alternative. The use of the cottontop marmoset as an experimental subject for elucidating the role of neutralizing antibodies in preventing the establishment of infection may be defended in terms of the animal's lack of immune responsiveness. Its suitability for studies of infection establishment and the usefulness of studies of isolation of individual membrane antigen components, a goal which is currently not feasible, are discussed. Viral subunit vaccination in primates is the first step in understanding the the interaction of EBV with the immune response during infection, which may eventually lead to preventive measures in man. (212 Refs)

10. PRODUCTION OF HEPATITIS B E ANTIBODY IN EPSTEIN-BARR VIRUS-INDUCED B LYMPHOCYTE CELL LINES.

Furuya Y, Inoue M, Yoshida Y, Yoshikura N, Takada M
Kanagawa Prefectural Public Health Lab., 52-2 Nakao-cho, Asahi-ku, Yokohama 241, Japan
J Med Virol; 9(4):293-297 1982

A specific antibody-producing lymphocyte cell line (LCL) was established from peripheral blood lymphocytes of a donor carrying hepatitis B e (HBe) antibody (anti-HBe). Cultures were depleted of T-cells by removal of erythrocyte-rosetting cells, and were subsequently infected in vitro with Epstein-Barr virus. Upon initial establishment of the LCL anti-HBe could not be detected by solid-phase radioimmunoassay (RIA), double immunodiffusion, or reverse passive hemagglutination inhibition (R-PHI). However, after centrifugal harvesting of cells rosetting with HBe antigen-coupled sheep red blood cells the 10-fold concentrated supernatant showed the presence of anti-HBe by all three methods after 1 wk. The anti-HBe titer was 64-fold at 1 wk, 256-fold at 2 wk, 128-fold at 3 wk, but undetectable at 5 wk using R-PHI. RIA could not detect anti-HBe after 5 wk either. Anti-HBe activity in the culture supernatant was not destroyed by treatment with 0.2 M 2-mercaptoethanol at 2 wk, indicating that the antibody was not sensitive to this agent. and that the anti-HBe was IgG. The decline in anti-HBe activity in long-term cultures was not associated with any change in growth pattern. (12 Refs)

11. HEPATITIS A VIRUS INFECTION OF HBSAG-PRODUCING HEPATOCELLULAR CARCINOMAS IN ATHYMIC MICE.

Gauss-Muller V, Deinhardt F, Hahn E, Lamerz R
Max von Pettenkofer Inst., Univ. Munich, Pettenkoferstrasse 9a, D-8000 Munchen 2, W. Germany
Cancer Immunol Immunother; 13(1):53-55 1982

Response of athymic mice bearing tumors of hepatocellular carcinoma (HCC) origin to infection with hepatitis A virus (HAV) and the production of HAV antigen (HAAg) in vivo were examined. Tumors were observed 25 days after inoculation in 17/23 mice when more than 2 x 10(7) PLC/PRF/5 or Hep 3B cells (of HCC origin) were injected. Histological examination of the tumors (originated by cell inoculation or tissue transplantation) revealed a morphology similar to that of differentiated primary HCC tumors. Neither antigens nor antibodies of the HBc or HBe system could be detected, but HBsAg or anti-HBs were found. (hepatitis B surface antigen) or anti-HBs were found. Sera of all mice bearing tumors were also positive for alpha-fetoprotein. PLC/PRF/5 cells in monolayer culture were infected with cell culture-adapted HAV. After 5 wk, when HAAg could be detected, the infected cells were suspended and inoculated into nude mice at a concentration of 5 x 10(7) cells/mouse. Only one of three mice developed a small nodule (100 mg wet wt) which was positive for HAAg. After transfer of tumor pieces to another series of mice, no mice grew tumors within 4 wk. Infectious virus (105TCD50) was inoculated directly into existing tumors. HAAg was found in six of eight inoculated tumors after 16-37 days. No significant relationship was observed between HAV injection and tumor growth in animals. When sera of HAV-infected tumor-bearing mice were tested for markers of HAV, neither antigen nor antibody was detected. (11 Refs)

12. A HUMAN HEPATOMA CELL LINE (PLC/PRF/5) PRODUCES LUNG METASTASES AND SECRETES HBSAG IN NUDE MICE.

Sattler FR, Paolucci S, Kreider JW, Ladda RL
500 University Drive, Hershey, PA, 17033
Eur J Cancer Clin Oncol; 18(4):381-389 1982

PLC/PRF/5 is a human liver cancer cell line which synthesizes hepatitis B virus surface antigen (HBsAg). These cells produced tumor in 6 of 8 (75%) congenitally athymic nude mice at 13 of 28 subcutaneous injection sites and in 13 of 14 (93%) mice inoculated intraperitoneally. Tumors were successfully transplanted to four of six additional nude mice. Tumor growth was rapid. Growth of cephalad tumors was significantly greater than for caudal tumors (0.39 mm/day vs 0.28 mm/day). Microscopic examination of tumors showed moderately well-differentiated hepatocellular carcinoma. Foci of identical cells were present in pulmonary veins in 7 of 14 tumor-bearing animals. Tumor cell karyotype was identical with that of PLC/PRF/5 cells. In addition, HBsAg was detectable in high titer in animals with extensive tumor. Biological features of PLC/PRF/5-induced tumors in nude mice appeared to closely resemble human hepatocellular carcinoma. Moreover, HBsAg may provide a marker of tumor growth. (Author abstract) (24 Refs)

13. A HIGHLY PREDICTABLE ANIMAL MODEL OF RETINOBLASTOMA.

Kobayashi M, Mukai N, Solish SP, Pomeroy ME
(c/o Mukai) Library, Eye Res. Inst., 20 Staniford St., Boston, MA, 02114
Acta Neuropathol (Berl); 57(2/3):203-208 1982

A highly predictable animal model in newborn inbred CDF rats is described that consistently provides young animals bearing retinoblastoma-like tumors in the vitreous cavity within 1 mo of tumor cell inoculation. The retinoblastoma-like cell line EXP-5 used was derived from an explant of fresh retinoblastoma-like neoplasms induced by adenovirus 12 (Ad 12) in eyes of syngeneic newborn rats. Within 1 mo after intravitreous inoculation of EXP-5 cells, a clinically recognizable ocular tumor was obtained in all 39 rats injected. Immunofluorescent techniques demonstrated Ad 12-specific tumor antigens in cultured tumor cells. Morphologic studies, including use of the light and electron microscope, indicated the tumor cells closely resembled retinoblastoma, with poorly differentiated intracytoplasmic organelles, solitary cilia with a 9 + 0 tubule pattern, and abnormal nuclear membrane associated with a set of basal bodies. A review is presented of transplantable retinal tumors described to date and compared to tumor cell line EXP-5. (15 Refs)

14. MAPPING OF A DNA-BINDING DOMAIN OF SIMIAN VIRUS 40 T-ANTIGEN USING NON-DEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Montenarh M, Deppert W, Henning R
Dept. Biochemistry, Univ. Ulm, P.O. Box 4066, 7900 Ulm, W. Germany
FEBS Lett; 142(1):129-132 1982

In the attempt to localize a nonspecific DNA-binding region in the polypeptide chain of tumor antigen (T-Ag), a comparison was made between the calf thymus DNA-binding properties of simian virus 40 (SV40) T-Ag from SV40-transformed human cells and T-Ag related polypeptides coded for by Ad+ND2 and Ad2+ND4. The study suggests a DNA-bind-

ing domain inside the polypeptide chain of T-Ag located between maximally 0.53 and 0.39 SV40 DNA map units. (21 Refs)

15. QUANTITATION OF A 55K CELLULAR PROTEIN: SIMILAR AMOUNT AND INSTABILILTY IN NORMAL AND MALIGNANT MOUSE CELL LINES.

Mora PT, Chandrasekaran K, Hoffman JC, McFarland VW
Macromolecular Biology Section, NCI, NIH, Bethesda, MD, 20205
Mol Cell Biol; 2(7):763-771 1982

Quantitative expression of a specific 55,000 mol wt (55K) cell protein was studied in two groups of mouse fibroblast (clonal) cells from two parental clones, one with high (HT), the other with low tumorigenicity (LT). From the LT clone, tumor lines and clones were obtained by selecting rare, spontaneously transformed highly tumorigenic (mutant) cells. Cells were labeled during exponential growth with 35S-methionine, and the 55K protein was immunoprecipitated with a monoclonal antibody and quantitated. There were low and approx equal amounts of 55K in cells (clones) with both low and high tumorigenicity from both groups of cells; there was no correlation between quantitative expression of 55K protein and cellular tumorigenicity. As shown previously, there was approx 10 to 20-fold more 55K protein in all simian virus 40 (SV40)-transformed T antigen-positive derivative clones. The T antigen-negative revertant tumor lines and clones obtained by an immunological in vivo selection method had low amounts of 55K protein, as in the parent cell before SV40 transformation. In all T antigen negative cells (including highly tumorigenic cells), degradation of the 55K protein was rapid, with a half-life of 15-60 min. The 55K protein was stable in all T antigen-positive cells (half-life greater than 10 hr). There was a very low, or an undetectable amount of the 55K protein in primary cells established from the tumors induced by highly tumorigenic cells. In contrast, primary cells obtained from early murine embryos had large amounts of (stable) 55K proteins. (30 Refs)

16. ASSOCIATION OF SV40 LARGE TUMOR ANTIGEN AND CELLULAR PROTEINS ON THE SURFACE OF SV40-TRANSFORMED MOUSE CELLS.

Santos M, Butel JS
(c/o Butel) Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX, 77030
Virology; 120(1):1-17 1982

A cellular protein with a mol wt of about 53,000 (53K) and histocompatibility antigens (mouse H-2 antigens) have been reported to be associated with viral-specified proteins in transformed cells. We investigated whether such associations could be detected on the surface of SV40-transformed mouse cells. A differential immunoprecipitation technique was adapted so that surface-associated antigens could be detected independently from intracellular antigens. The precipitated proteins were eluted and analyzed by SDS-polyacrylamide gel electrophoresis. Reconstruction experiments established that SV40 large T antigens (T-ag) released from the nucleus during the extraction procedure was not combining with free antigen-binding sites on antibodies bound to the cell surface in the external reaction, that nuclear unbound T-ag was not exchanging with bound surface antigen during extraction, and that the surface reaction was not due to nuclear T-ag released from dead cells and non-specifically adsorbed onto the surface of living cells. It appears that SV40 large T-ag and cellular 53K protein are associated on the surface as well as within SV40-transformed mouse cells. In contrast, no detergent-stable complex between T-ag and mouse H-2 antigens was detected on the transformed cells. The possibility that molecular interactions between viral- and cell-coded proteins could be involved in determining some of the observed transformation-related cellular phenotypic changes is discussed. (73 Refs)

17. DISCRETE REGIONS OF SIMIAN VIRUS 40 LARGE T ANTIGEN ARE REQUIRED FOR NONSPECIFIC AND VIRAL ORIGIN-SPECIFIC DNA BINDING.

Prives C, Barnet B, Scheller A, Khoury G, Jay G
Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
J Virol; 43(1):73-82 1982

The nondefective adenovirus Type 2 (Ad2)-simian virus 40 (SV40) hybrid viruses, Ad2+ND2 and Ad2+ND4, have been used to determine which regions of the SV40 genome coding for the large tumor (T) antigen are involved in specific and nonspecific DNA binding. Ad2+ND2 encodes 45,000 Mr (45K) and 56,000 Mr (56K) T antigen-related polypeptides. The 45K polypeptide did not bind to DNA, but the 56K polypeptide bound nonspecifically to calf thymus DNA. Ad2+ND4 encodes 60,000 Mr (60K), 66,000 Mr (66K), 70,000 Mr (70K), 74,000 Mr (74K), and 90,000 Mr (90K) T antigen-related polypeptides, all of which bound nonspecifically to calf thymus DNA. However, in more stringent assays, where tight binding to viral origin sequences was tested, only the 90K protein specified by Ad2+ND4 showed specific high affinity for sequences at the viral origin of replication. From these results and previously published experiments describing the SV40 DNA integrated into these hybrid viruses, it was concluded that SV40 early gene sequences located between 0.39 and 0.44 SV40 map units contribute to nonspecific DNA binding, whereas sequences located between 0.50 and 0.63 SV40 map units are necessary for specific binding to the viral origin of replication. (Author abstract) (41 Refs)

18. CV-1 CELLS RELEASE PROTEINS THAT FACILITATE INFECTION BY SIMIAN VIRUS 40 AND ECHOVIRUS 6.

Righthand VF, Bagshaw JC
Dept. Immunology and Microbiology, Wayne State Univ. Sch. Medicine, Detroit, MI, 48201
Arch Virol; 72(1/2):55-66 1982

Uninfected simian cells (CV-1) produce two different proteins, one of which enhances the infectivity of echovirus 6 and the other enhances the infectivity of SV40 in less susceptible cells. The enhancers are released by metabolizing cells into the culture medium. The SV40 enhancer protein is larger and less acidic than the echovirus enhancer. The SV40 enhancer protein can be dissociated into two subunits with apparent mol wt of 42,000 and 24,000. The echovirus enhancer protein consists of two subunits with apparent mol wt of 28,000 and 31,000. Electrophoretically purified enhancer proteins interact with virions and retain their biological activities and viral specificities. The SV40 enhancer stimulates expression of SV 40-T antigen under conditions in which untreated virus does not initiate expression of T antigen. This result and the observation that the enhancers do not increase the infectivity of the nucleic acids of their respective viruses suggest that the enhancers act either at the stage of penetration or uncoating. (Author abstract) (13 Refs)

19. A SMALL SUBCLASS OF SV40 T ANTIGEN BINDS TO THE VIRAL ORIGIN OF REPLICATION.

Scheller A, Covey L, Barnet B, Prives C
Dept. Biological Sciences, Columbia Univ., New York, NY, 10027
Cell; 29(2):375-383 1982

We examined the affinities of SV40 large T antigen for unique viral DNA sequences by binding SV40 Bst NI DNA fragments in extracts of infected or transformed cells, and then immunoprecipitating the T antigen-DNA complex. The G fragment, which spans the viral origin of replication (ori) was quantitatively bound to T antigen. A T-antigen-specific monoclonal antibody (Mcl 7), which recognized only 5%-10% of the T antigen from infected or transformed cells, immunoprecipitated the majority of the ori-binding activity. This suggests that only a minor subclass of wild-type T antigen is active in binding to the origin. C6 cells contain a replication-defective mutant T antigen that when tested in the DNA-binding immunoassay, showed no affinity for the ori fragment. Mcl 7 not only failed to immunoprecipitate ori binding in C6 cells, but also did not detect any labeled C6 T antigen whatever. Thus Mcl 7 recognizes an immunologically distinct subset of wild-type T antigen that comprises the origin-binding form of the viral protein, which is absent in the C6 T antigen population. Mcl 122, which recognizes a 53 kilodalton host protein that complexes with T antigen, immunoprecipitated ori-binding activity from extracts of infected or transformed cells, but not from C6 cells. Thus wild-type T antigen can bind ori sequences even when complexed to the host protein. These data suggest that T antigen consists of different subpopulations with different functions. (Author abstract) (48 Refs)

20. ISOLATION AND CHARACTERIZATION OF SIMIAN VIRUS 40 EARLY REGION DELETION MUTANTS.

Sompayrac LM, Danna KJ
Dept. Molecular, Cellular and Developmental Biology, Univ. Colorado, Boulder, CO, 80309
J Virol; 43(1):328-331 1982

We constructed a tsB4/dl884 double-mutant helper virus and used it to isolate two simian virus 40 early region deletion mutants that lack about half of the DNA sequences normally used to encode the large tumor antigen (T). Both mutants make a normal-sized small t antigen, but neither mutant can replicate its DNA in the absence of a T+ helper. (Author abstract) (15 Refs)

21. PURIFICATION OF POLYOMA VIRUS MEDIUM-SIZE TUMOR ANTIGEN BY IMMUNOAFFINITY CHROMATOGRAPHY.

Walter G, Hutchinson MA, Hunter T, Eckhart W
Institut fur Immunbiologie der Albert-Ludwigs-Universitat, 7800 Freiburg im Breisgau, W. Germany
Proc Natl Acad Sci USA; 79(13):4025-4029 1982

We have used antibodies against the synthetic peptide Lys-Arg-Ser-Arg-His-Phe, corresponding to the six COOH-terminal amino acids of the polyoma virus medium tumor (T) antigen, to purify the medium T antigen by affinity chromatography. Release of the medium T antigen from the anti-peptide antibody was achieved under mild conditions by using a large excess of the peptide in an isotonic buffer at neutral pH containing mixed detergents. This procedure yielded a 2,500-fold purification of the medium T antigen in a single step. The protein kinase activity associated with the medium T antigen was also released and was studied in this active state in solution. Sedimentation analysis showed that the bulk of the purified medium T antigen was in a monomeric form (Mr about 42,000) not associated with protein kinase activity. A small fraction of the medium T antigen was found in a rapidly sedimenting form (Mr about 200,000) that possessed protein kinase activity. (Author abstract) (26 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

22. THE PATHOGENESIS OF ABELSON VIRUS LYMPHOMAS OF THE MOUSE.

Risser R
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Biochim Biophys Acta; 651(4):213-244 1982

The origin of the Abelson virus (AV) and the pathogenesis of the disease it induces are discussed. Before discussing Abelson murine leukemia virus (A-MuLV) in detail, some insights gained from the study of other RNA tumor viruses, both with respect to mechanisms of their action and host genetic responses to them, are presented. The main presentation comprises four sections. Virological and molecular characterization of AV involves its isolation, assays, genome structure of the helper and defective viruses, proteins encoded by the defective A-MuLV genome, and mutants of AV. Biology of AV diseases is discussed in relation to transformation of bone marrow cells by A-MuLV and pathogenesis. Differentiative phenotype of Abelson lymphomas and cell lines is discussed in relation to phenotypes of in vitro-derived lines, expression of lineage markers by tumors, and neoplastic differentiation of clonal Abelson lymphoma lines. With relation to cellular antigens identified on Abelson lymphoma and transformed cells, Abelson target-associated antigen, p50 and Abelson lymphoma antigens are discussed. A final section presents a summary of present knowledge, interpretations and further speculations on the involvement of AV in hematopoietic differentiation and neoplasia. (187 Refs)

23. DETECTION OF ACQUIRED PROVIRUS SEQUENCES IN MAMMARY TUMORS FROM LOW-EXPRESSOR, LOW-RISK MICE.

Altrock BW, Cardiff RD, Puma JP, Lund JK
(c/o Cardiff) Dept. Pathology, Sch. Medicine, Univ. California, Davis, Davis, CA, 95616
JNCI; 68(6):1037-1041 1982

Murine mammary tumor virus (MuMTV) provirus sequences in the DNA from early-occurring (av age 10 mo) and late occurring (age greater than 20 mo) tumors in BALB/cfC3H mice were analyzed by Eco RI restriction endonuclease mapping procedures. All early tumors were MuMTV antigen-positive mammary adenocarcinomas that contained the 0.92-and 4.0-kilobase (kb) exogenous C3H MuMTV-specific Pst I restriction endonuclease fragments. All but one of the late mammary adenocarcinomas had MuMTV antigens detected by peroxidase antiperoxidase staining, and all contained the 0.92-and 4.0-kb exogenous virus Pst I fragments. Three late nonmammary tumors lacked both MuMTV antigens and acquired provirus sequences. Greater numbers of MuMTV sequences were detected in both early and late-arising mammary tumors by Eco RI restriction endonuclease mapping than were detected in tissues from uninfected BALB/c mice. However, neither the

number nor the location of MuMTV proviruses correlated with tumor latent period. (Author abstract) (19 Refs)

24. RADIOIMMUNOASSAY FOR MAJOR EXTERNAL GLYCOPROTEIN OF MURINE MAMMARY TUMOR VIRUS.

Chiplunkar SV, Karande KA
Dept. Immunology, Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 20(2):121-125 1982

A radioimmunoassay assay is described in which highly purified intact murine mammary tumor virus (MuMTV) virions from the expressed milk of strains C3H(Jax) and ICRC mice were externally labeled with 125I in the presence of lactoperoxidase. Heterologous polyvalent antisera prepared against disrupted virions were used for immunoprecipitation. Sodium dodecyl sulfate polyacrylamide electrophoresis showed that both iodinated virions migrated as a single peak with an estimated mol wt of 49,000 daltons. This peak corresponds to the previously described major membrane glycoprotein (gp 49) of MuMTV. Competition radioimmunoassays using antisera to MuMTV C3H and MuMTV ICRC with their respective labeled virions were shown to be specific for MuMTV antigens. Tissue extracts of C57BL liver and lactating mammary gland, ICRCf liver, swiss mouse milk plasma and fetal calf serum proteins did not compete in the assay. The addition of 4 ug of unlabeled MuMTV ICRC completely inhibited the binding of anti-MuMTV ICRC serum to 125I-labeled MuMTV ICRC. Large amounts of gp 49 were found in tumor extracts (940-3,937 nanog/mg) and sera (160-680 nanog/ml) of C3H and ICRC tumor-bearing mice. The assay can detect 3 nanog of antigen and is highly reproducible. (29 Refs)

25. THE ROLE OF VIRAL AND ONCOFETAL ANTIGENS IN MURINE LYMPHOSARCOMA METASTASIS TO SPECIFIC SITES (MEETING ABSTRACT).

Nicolson GL, Reading CL, Mascali JJ, McGuire EJ
Department of Tumor Biology, The University of Texas Cancer Center System, M. D. Anderson Hospital and , Tumor Institute Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:181 1982

Metastatic variants of murine RAW117 lymphosarcoma were established by sequential selection in vivo for enhanced liver or lung colonization or in vitro for decreased binding to the immobilized-lectins Con A, WGA, RCA (concanavalin A, wheat germ agglutinin, red cell agglutinin) and PNA. The heterogeneity and stability of the selected sublines were examined using cloning techniques. Cell surface analysis of sublines and clones indicated that loss of cell surface viral envelope glycoprotein gp70 correlated well with metastatic properties suggesting that host response may be involved. A variety of in vivo experiments indicated that host macrophages may suppress high gp70 containing clones but allow growth of low gp70 containing clones. To determine the role of cell surface oncofetal antigens in organ colonization we tested the effects of antibodies made against fetal liver cell adhesion components. Liver specific colonization was blocked by pretreatment with Fab' or F(ab')2 antibodies made against the embryonic liver cells. The liver colonizing RAW117 sublines appear to have higher levels of the oncofetal antigen(s) compared to parental or lung colonizing tumor cells. (2 Refs)

26. REGULATION OF THE EXPRESSION OF MOUSE MAMMARY TUMOR VIRUS (MMTV) GP52 EPITOPES (MEETING,ABSTRACT).

Tax A, Manson LA
The Wistar Institute, Philadelphia, PA, 19104
Proc Am Assoc Cancer Res; 23:1096 1982

We have applied the lymphocyte hybridoma technology to analysis of the tumor specific antigens displayed on a progressively growing tumor, Mm5mt/c1, which secretes mouse mammary tumor virus (MMTV). To date, all the cloned lymphocyte hybridomas that have been obtained from tumor-bearing animals (rats and C3H/f/C57BL/6 mice) secreting monoclonal antibodies (MCA) directed specifically against this tumor, react with the gp52 of MMTV, the major coat antigen of MMTV. Seven secrete an IgG antibody, whereas four secrete an IgM antibody. Two of the three rat MCA's react with antigenic determinants on the gp52 molecule that are sensitive to NP40. The epitopes with which the other nine MCA's react are stable to NP40. Specificity tests have shown that one MCA is relatively specific for C3H-MMTV and reacts poorly with RIII-MMTV suggesting it may be strain-specific. Three have been found to cross-react completely with both strains of MMTV and are therefore group-specific. Several examples of studies of the expression of the gp52 epitopes using these MCA's as analytical tools, in normal mice, and in tumor-bearing animals as well as studies with species other than the mouse will be shown. (no Refs)

27. ROUS SARCOMA VIRUS TRANSFORM HUMAN NORMAL FIBROBLASTS AND 'SUPERTRANSFORM' HUMAN SARCOMA CELLS (MEETING ABSTRACT).

Rabotti G, Teutsch B, Mongiat F, Mariller M
Laboratoire de Medecine Experimentale, College de France, 11 Place Marcelin Berthelot, 75231 Paris Cedex 05, France
Proc Am Assoc Cancer Res; 23:99 1982

Sixty cell lines of human fibroblasts originating from 60 different donors were infected with various strains of Rous Sarcoma Virus (RSV). Two cell lines were successfully transformed. This was achieved with one strain of virus only: Schmidt-Ruppin RSV (Sr RSV subgroup B). The virus was recovered upon co-cultivation of the transformed cells with susceptible chicken fibroblasts (CEF). Suprisingly these cells were found to produce viral particles as demonstrated by infectivity assays of filtered supernatant. The avian transforming virus produced by human cells has the typical type C morphology and some of the antigenic proteins of RSV. Cell-lines of undifferentiated sarcomas originating from 6 different patients were also infected with the same strains of RSV. One cell line was successfully 'supertransformed' it was virogenic (upon co-cultivation with CEF) and produced infectious virus. This is the first demonstration of transformation of human normal fibroblasts by an avian retrovirus. The data showing that only 2 out of 60 cell phenotypes and 1 out of 6 sarcoma cell lines were transformed suggest that susceptibility to RSV transformation in human cells is genetically controlled. Since in their natural hosts these viruses are known to recombine with cellular information it is possible that a similar event takes place here and that recombination of RSV with human cellular sequences may occur in this virus produced in human cells. (no Refs)

28. DIFFERENTIAL SUSCEPTIBILITY OF HUMAN CELLS TO TRANSFORMATION BY MURINE AND AVIAN SARCOMA VIRUSES.

Rhim JS, Trimmer R, Huebner RJ, Papas Ts, Jay G
NCI, NIH, Bethesda, MD, 20205
Proc Soc Exp Biol Med; 170(3):350-358 1982

The susceptibility of human skin fibroblasts from patients with adenomatosis of the colon and rectum (ACR) and Gardner's syndrome and of human osteosarcoma clonal cells to Kirsten murine sarcoma virus (KiMSV) and Rous sarcoma virus (RSV) was investigated. Results obtained confirmed a previous report that skin fibroblasts from individuals genetically predisposed to colorectal cancer were preferentially transformed by KiMSV. The human osteosarcoma clonal cells infected with RSV showed altered morphology, increased growth rate, higher efficiency of colony formation in soft agar, growth of larger aggregates and growth in aggregate form above an agar base, and tumorigenicity in nude mice. The transformed cells produced neither RNA-dependent DNA polymerase nor type C virus particles; however, the transformed cells contained RSV CF antigen and a rescuable infectious virus. The transformed cells also contained an RSV transformation specific protein p60src-associated kinase activity. (22 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

29. DETECTION OF POLYOMA-VIRUS-INDUCED TUMOR ANTIGEN(S) BY MACROPHAGE MIGRATION INHIBITION.

Szigeti R, Dalianis T, Klein G, Ito Y, Magnusson G
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm, Sweden
Int J Cancer; 30(1):69-74 1982

We have applied the macrophage migration inhibition assay to study cell-mediated immune responses to antigens of polyoma-virus-transformed cells. Macrophages from polyoma-virus-immunized mice, but not from control mice, showed significant migration inhibition when exposed to extracts of polyoma-virus-induced mouse and rat transformed cells. Extracts of non-polyoma-induced tumors had no such effect. (Author abstract) (31 Refs)

30. TUMORIGENICITY OF SV40-TRANFORMED HUMAN CELLS IN IMMUNODEFICIENT MICE (MEETING ABSTRACT).

Choi KH, Kaha P, Shin SI
Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, 10461
Proc Am Assoc Cancer Res; 23:95 1982

Neoplastic transformation of mammalian cells in vitro by the simian papova virus SV40 is widely used as an experimental model of viral oncogenesis. It was shown prevously that rodent cells transformed by SV40 to the anchorage-independent state form progressively growing tumors in athymic nude mice. In contrast, human cells similarly transformed by SV40 rarely form tumors in this host. To determine whether their failure to form tumors is due to rejection by a thymus-independent mechanism in the athymic host, the tumorigenicity of a cloned SV40-transformed human cell line designated SV80 was examined in BALB/c nude mice under a variety of conditions. We found that SV80 cells can grow as tumors if they are injected sc into immature CBA/N nude mice or if they are repeatedly injected ip into newborn BALB/c nude mice over a period of 3 weeks. In the latter case, all mice (8/8) developed widespread metastatic nodules in the peritoneal and thoracic cavities. Somatic cell hybrids produced by fusing SV80 cells with a highly tumorigenic clone of HeLa cells were also found to be nontumorigenic in BALB/c nude mice, but hybrid cells not expressing the virus-coded tumor (T) antigens were tumorigenic in the same host. These and additional related data support the hypothesis that at least some human cells transformed by SV40 are inherently tumorigenic, and that these cells are unable to form growing tumors in nude mice because of the existence of a thymus-independent tumor rejection mechanism. (no Refs)

31. LEUKOCYTE MIGRATION INHIBITION INDUCED BY EPSTEIN-BARR VIRUS ANTIGENS. IMMUNITY IN INFECTIOUS MONONUCLEOSIS AND SOME IMMUNODEFICIENT AND IMMUNOSUPPRESSED STATES.

Szigeti R, Klein E, Masucci MG, Ernberg I, Svedmyr E, Klein G
II. Gyermekklinika, Semmelweis Orvostudomany Egyetem, Budapest, Hungary
Orv Hetil; 123(20):1217-1221 1982

Leukocyte migration inhibition (LMI) elicited by Epstein-Barr virus (EBV) antigens was studied in 13 patients with infectious mononucleosis (IM), 2 patients with chronic mononucleosis, 4 with sex-linked lymphoproliferative disease and in 12 patients with neoplastic diseases (5 with Hodgkin's disease, 6 with non-Hodgkin's lymphoma and 1 with chronic lymphocytic leukemia). Appreciable LMI was observed in the patients with IM in response to enriched early antigen-virus capsid antigen (EA/VCA) extracts. Similar LMI of mononucleosis type (sensitivity to EA/VCA and insensitivity to EBV nuclear antigen (NA)) was seen in chronic mononucleosis as well, while the patients with sex-linked lymphoproliferative disease failed to respond to any EBV antigens. Tumor patients with elevated EBV antibody titers either showed LMI similar to that seen in healthy, seropositive controls or LMI of the mononucleosis type. The findings suggest that an intact immune system is necessary for LMI to occur in response to EBVNA or to crude cellular extracts containing mainly EBVNA, while sensitivity to EA/VCA is present when the immune system is impaired to a certain extent. Late hypersensitivity reaction in vitro is absent in severe immunodeficiency or immunosuppression. (42 Refs) (In HUN)

32. LYSIS OF AUTOLOGOUS EPSTEIN-BARR VIRUS-INFECTED B CELLS BY CYTOTOXIC T LYMPHOCYTES OF RHEUMATOID ARTHRITIS PATIENTS.

Tsoukas CD, Carson DA, Fong S, Slovin SF, Fox RI, Vaughan JH
Dept. Clinical Res., Scripps Clinic Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
Clin Immunol Immunopathol; 24(1):8-14 1982

Since B lymphocytes of patients with rheumatoid arthritis (RA) have a higher rate of Epstein-Bar virus (EBV)-induced transformation than normal B cells, we have investigated whether this phenomenon is related to defective cytotoxic T-cell control of emerging B-cell clones. We have studied the in vitro generation of cytotoxic T lymphocytes specific for antigens appearing on autologous B cells after EBV infection using lymphocytes from six patients with RA. Cytotoxic cells were generated by two cycles of stimulation with mitomycin C-

treated autologous B cells, and their lytic activity was assessed against 51Cr-labeled targets. As previously reported for lymphocytes of normal individuals, RA cytolytic T lymphocytes were induced only by EBV-infected B cells, not by noninfected B cells, and expression of the cytotoxicity required EBV-transformed targets. After primary in vitro stimulation with autologous EBV-infected B cells, the RA cytotoxic cells expressed higher lytic activity than the normal counterparts, but the difference was not statistically significant (p greater than 0.1). However, after secondary in vitro stimulation both groups displayed similar cytotoxic activities. In the presence of complement, monoclonal antibodies OKT8 (characterizing cytotoxic/ suppressor cells), SC1, and OKT3 (characterizing most T cells) reduced cytotoxicity by 80-90%; antibody OKT3 also reduced the lytic activity by 68% in the absence of complement. We conclude that the higher EBV-induced transformation rate seen with RA lymphocytes is not explained by a deficiency in this EBV-specific cytotoxic T cell. (Author abstract) (29 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

33. MAMMARY TUMOR INDUCTION IN INBRED MOUSE STRAINS WITH URETHANE IS NOT ACCOMPANIED BY CHANGES IN EXPRESSION OF B- AND C-TYPE RETROVIRAL STRUCTURAL PROTEINS.

Imai S, Morimoto J, Tsubura Y, Hilgers J
Dept. Pathology, Nara Medical Coll., 840 Shijo-cho, Kashihara-shi, Nara-ken 634, Japan
Int J Cancer; 30(1):101-106 1982

Urethane administered in the drinking water of breeding female mice of five inbred strains (DDf, KF, C3Hf, ddY and C57BL) leads to a higher incidence of mammary tumors at an extremely early age in four of these strains (DDf, KF, C3Hf and ddY). In the case of the DDf strain the tumors are adenoacanthomas, but in the case of the other strains adenocarcinomas are also observed. The effect of urethane in the drinking water on expression of endogenous retroviral structural proteins of the B and C type (MTV and MuLV) was studied in the milk by an immunodiffusion test and in organ extracts by radioimmunoassays (for MTVp27, MTVgp52 and MuLVp30). Organs tested include salivary glands, thymus and spleen from female and male animals. In addition, prostate and seminal vesicles were tested in male animals and uterus and mammary glands in females. Mammary tumors induced by urethane were also tested. Urethane does not induce or enhance endogenous retroviral antigen expression, either in these organs or in the mammary gland, one of the target organs for tumorigenesis by this agent. (Author abstract) (34 Refs)

34. INDUCTION OF SYNTHESIS OF EPSTEIN-BARR VIRUS DNA AND VIRUS-SPECIFIC POLYPEPTIDES BY TUMOR PROMOTER IS ENHANCED BY NON-PROLIFERATIVE STATE OF CELLS (MEETING ABSTRACT).

Lin JC, Smith MC, Pagano JS, Feighny RJ
Cancer Research Center, University of North Carolina, Chapel Hill, NC, 27514
Proc Am Assoc Cancer Res; 23:2 1982

TPA (12-0-tetradecanoylphorbol-13-acetate) is a potent inducer of Epstein-Barr Virus (EBV) gene expression. The magnitude of activation of latent EBV genome by TPA depended upon the physiological state of the cells when they were exposed to drug. While TPA was able to induce EBV genome replication in P3HR-1 cells in all phases of growth, the most dramatic increase in viral genome copies per cell occurred in nonproliferative cells as opposed to cells in exponential growth. Early antigen (EA) synthesis in nonproliferative Raji cells activated by TPA increase 300-fold in contrast to only 100-fold increase in exponentially growing cells treated with TPA. The marked enhancement in activation of latent EBV genomes and marked reduction in cellular protein synthesis in nonproliferative cells treated with TPA makes it possible for direct detection of virus-specific polypeptides associated with activation. Analysis of polypeptides synthesized in TPA - induced P3HR-1 cells by immunoprecipitation indicated that polypeptides of 155K, 140K, 90K, and 78K were induced by TPA, whereas 145K, 120K, 92K, 80K, 75K, 72K, 68K, 65K and 50K were polypeptides present in spontaneously induced P3HR-1 cells not treated with TPA. At least eleven polypeptides (90K, 80K, 75K, 52K, 46K, 45K, 43K, 40K, 38K, 35K, and 33K) were clearly detected in TPA-induced Raji cells. The insensitivity of these polypeptides to acyclovir and their appearance paralleling EA induction lead us to conclude that at least some are components of EA. (no Refs)

35. INTERFERON INDUCTION IN HEALTHY AND TUMOR-BEARING DOGS BY CELL WALLS OF MYCOBACTERIUM BOVIS STRAIN BACILLE CALMETTE-GUERIN.

Winters WD, Harris SC
Dept. Microbiology, Univ. Texas Health Science Center San Antonio, San Antonio, TX, 78284
Am J Vet Res; 43(7):1232-1237 1982

High titers of interferon (IF) were released into the circulation of 8 of 10 adult, female, healthy dogs (Group A) and 7 of 10 pet dogs (Group C) bearing naturally occurring primary malignant mammary tumors after they were given a single dose (4 mg/ml) of a Mycobacterium bovis bacille Calmette-Guerin cell wall (BCG-CW) emulsion. This BCG-CW emulsion had been administered into one mammary gland in the 10 healthy dogs and intratumorally in the 10 dogs bearing biopsy-confirmed malignant mammary tumors. Increases in IF titers were not detected in sera from 10 dogs (Group D) bearing malignant mammary tumors injected with placebo, from 10 dogs (Group E) after surgical excision of malignant mammary tumors, and from 15 noninjected healthy control dogs (group B). The IF detected in the sera of tumor-bearing and healthy dogs following injection of BCG-CW was effective against vesicular stomatitis virus and influenza A virus when tested in Madin-Darby canine kidney cells, but not in human KB cells. Vesicular stomatitis viral antibody was not detected by neutralization tests nor radioimmunoassays in sera from the subjects. At entry into the study of 30 dogs with malignant mammary tumors (Groups C, D, and E) and of 25 healthy dogs (Groups A and B), titers of IF were detected in 14 of the former and in 1 of the healthy dogs. There was no correlation between the pretreatment IF titers in tumor-bearing dogs and age, clinical history, breed, previous pregnancies, or tumor vol. In tumor-bearing dogs injected with BCG-CW (Group C), there was no apparent relationship between the induction of high titers of IF and any previously mentioned factors, the amount of BCG-CW injected, or serum levels of antibody specifically reactive with BCG-CW or canine viral antigens. (Author abstract) (37 Refs)

OTHER RELATED STUDIES

36. THE INFECTIONS MONONUCLEOSIS DOWNEY CELL POPULATION AND PAUL-BUNNELL ANTIGEN/ ANTIBODY (MEETING ABSTRACT).

Fjelde A, Rebolt O, Kellam J, Bennett P
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:1079 1982

In conjunction with previous studies with F Milgrom and K Kano, of the Paul-Bunnell (PB) heterophile system, in which we demonstrated the presence of PB antigen in (40%) human lymphoma-leukemia (LL) spleens, we studied the abnormal Downey cells found in IM along with PB antibodies, the antigen to which is considered to be unknown. We postulated that PB antigen is a neo-antigen arising as a result of B cell infection and is related to the benign nature of IM. Paul and Bunnell described PB antibody in 1932 and Downey and McKinley described IM lymphocytes in 1923. Since then the abnormal (Downey) lymphocytes and PB antibody have been considered diagnostic for IM. Using acute phase IM blood, we employed cell separation and identification techniques, to obtain purified or enriched cell populations. We found, in absolute values, a low increase in the B cell population and a high increase of T cells, depending on the lymphocytes/mm3. We were unable to detect PB antigen in IM peripheral blood lymphocytes. EBV (Epstein-Barr virus) believed to cause IM, infects B cells which during maturation develop virus receptor sites and in culture proliferate as established lines. T cells have finite life unless the culture media contains a growth factor. In vivo the Downey cell population consists of 'reactive' T cells, giving rise to the terminology 'self-limiting leukemia' to IM. A double immune system, the PB heterophile and the EBV, exists in IM patients. PB antibodies disappear during convalescence, but PB antigen is found in LL patients. (no Refs)

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VIRUS-RELATED ANTIGENS AND HUMAN CANCER

1. EXPRESSION OF HERPES SIMPLEX VIRUS TYPE 2 ANTIGENS IN PREMALIGNANT AND MALIGNANT HUMAN VULVAR CELLS.

Cabral GA, Marciano-Cabral F, Fry D, Lumpkin CK, Mercer L, Gopierud D
Dept. Microbiology, Medical Coll. Virginia, Virginia Commonwealth Univ., Box 678-MCV Station, Richmond, VA, 23298
Am J Obstet Gynecol; 143(6):611-619 1982

Vulvar biopsies and explants from patients with vulvitis, hyperkeratosis, condyloma acuminatum, severe dysplasia, and squamous cell carcinoma were screened for herpes simplex virus Type 2 (HSV-2) antigens. Immunoperoxidase staining for VP143, an early nonstructural polypeptide of HSV-2, was identified within three biopsies exhibiting severe dysplasia, three of seven with carcinoma in situ, and one of three with invasive squamous cell carcinoma. Similar staining for VP143 was observed in derived explants. Staining for VP119, the major envelope glycoproteins of HSV-2, was identified within tissues which were positive for VP143. Both proteins were ex-

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pressed in the absence of staining for virus capsid proteins, detection of virus structures by electron microscopy, and isolation of infectious virus by co-cultivation, indicating that only a fragment of the virus genome was expressed. Neither VP143 nor VP119 was identified in biopsies exhibiting vulvitis, hyperkeratosis, or condyloma acuminatum. These data indicate a close relationship between HSV-2 and vulvar neoplasia. (Author abstract) (19 Refs)

2. STUDY OF ANTIBODIES TO ADENOVIRUSES IN PATIENTS WITH TUMORS OF THE UROGENITAL SYSTEM.

Csata S, Kulcsar G, Horvath J, Nasz I, Ongradi J, Verebelyi A
Dept. Urology, Istvan Municipal Hosp., Budapest, Hungary
Int Urol Nephrol; 14(2):115-119 1982

Assays for antibodies to adenoviruses (AV) were conducted on approx 4,000 samples of sera from 516 patients including 193 with non-neoplastic diseases of the urogenital system, 253 with urogenital tumors, and 70 with nonurological organic diseases. Malignant tumors included 57 bladder, 32 prostatic, 15 renal, 15 testicular, and 23 other tumors. Benign tumors included 18 papillomas of the bladder, 4 urethral polyps, and 89 hypertrophies of the prostate. Antibodies were measured by the complement fixation reaction. Viruses and early antigens tested included AV Type 1 and 5 (of latent properties), AV Type 12 and 18 (of oncogenic capacity), and early non-virion antigens of AV Type 1, 5, 12, and 18. HEp cell extract served as a control. Results were similar for AV-1 and AV-5 and for AV-12 and AV-18. Complete AV-1 was found in 19% of the patients with urogenital tumors, 34% of the patients with non-neoplastic urogenital disease, and 12% of the patients with nonurological disease. The respective occurrences of early AV-1 antigens were 56%, 23%, and 33%. The respective occurrences of complete AV-12 antigens were 13%, 6%, and 2%. The respective occurrences of early AV-12 antigens were 53%, 18%, and 4%. Antibodies to non-virion antigens of oncogenic AV were thus more common in patients with urogenital tumors than in other patients, suggesting that defective forms of oncogenic AV are present and operating in many tumor patients. Antibodies of AV of latent character were more common among patients with non-neoplastic diseases. Data suggest that oncogenic AV are involved in tumors of the urogenital system. (24 Refs)

3. TREATMENT OF NASOPHARYNGEAL (NPC) CARCINOMA WITH INTERFERON: EPSTEIN-BARR VIRUS (EBV) SEROLOGY AND CLINICAL RESULTS OF A PILOT STUDY (MEETING ABSTRACT).

Connors JM, Andiman WA, Merigan TC, Savage ME, Liu E, Jacobs C
Stanford University School of Medicine, Stanford, CA, 94305
Proc Am Soc Clin Oncol; 1:C-771 1982

The purpose of this study was to determine the efficacy of human leukocyte interferon (alpha-IFN) in the treatment of NPC and its effect on IgA and IgG anti-EBV Viral Capsid Antigen (VCA), IgG and IgA Early Antigen (EAD), and oral excretion of EBV. Seven patients with recurrent NPC were studied. The mean age was 43 and the median performance status was 60. All patients had prior radiotherapy, and three patients had prior chemotherapy. Three had local/regional disease recurrence, and 4 had distant metastases. Alpha-IFN, was given at a dose of 10 X 10(6) units intramuscularly daily for 30 days. The mean IFN level 4-6 hours following injection was 190 units/ml (70-300 units/ml). The following anti-EBV serologic tests were monitored before, during, and after treatment: IgA-VCA, IgG-VCA, IgG-EAD and IgA-EAD. Titers ranged from 1:10-1:320 and did not change with treatment. Five patients were tested for oral excretion of EBV before and during IFN treatment. No patients excreted virus at any time. Treatment outcomes were as follows: 3 patients developed progressive disease after 22, 23 and 30 days of IFN; 3 had stable disease, but 2 of these did not complete a full course due to toxicity; 1 patient had a 90% reduction in tumor size of 1 month's duration. Toxicity included fatigue and fever in all patients, neutropenia in 1 patient. (no Refs)

4. CYTOMEGALOVIRUS AND KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN.

Drew WL, Miner RC, Ziegler JL, Gullett JH, Abrams DI, Conant MA, Huang ES, Greundwater JR, Volberding P, Mintz L
Dept. Pathology and Lab. Medicine, Mount Zion Hosp. and Medical Center, P.O. Box 7921, San Francisco, CA, 94120
Lancet; 2(8290):125-127 1982

Ten homosexual men with Kaposi's sarcoma (KS) were studied for evidence of cytomegalovirus (CMV) infection. IgG and IgM antibodies to CMV were detected in nine out of nine and in seven out of nine of these patients, respectively. CMV was recovered from body secretions or peripheral blood of seven patients. Viral cultures of KS tumor biopsy specimens were negative in eight out of eight patients, but CMV RNA was detected by in-situ hybridization in two out of three and CMV antigen(s) by immunofluorescence in six out of nine. Normal tissue specimens from three KS patients were negative for CMV antigen. These observations suggest an association of CMV with KS. (Author abstract) (25 Refs)

5. ACQUIRED IMMUNODEFICIENCY AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Geerling J
Afdeling Inwendige Ziekten, Slotervaartziekenhuis, Amsterdam, The Netherlands
Ned Tijdschr Geneeskd; 126(14):631-633 1982

Recent studies on the sudden increase in the incidence of Kaposi's sarcoma mostly in homosexual men abusing drugs are reviewed. The new syndrome is characterized by very poor prognosis and high incidence of infectious disease indicative of impaired cell-mediated immunity. Kaposi's sarcoma is believed to be of viral etiology. Human leukocyte antigen Dr 5 was found in 10/12 patients examined, while the frequency of this antigen is only 12% in the general population. (7 Refs) (In DUT)

6. HEALTHY CARRIERS OF A HUMAN RETROVIRUS, ADULT T-CELL LEUKEMIA VIRUS (ATLV): DEMONSTRATION BY CLONAL CULTURE OF ATLV-CARRYING T CELLS FROM PERIPHERAL BLOOD.

Gotoh YI, Sugamura K, Hinuma Y
Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan
Proc Natl Acad Sci USA; 79(15):4780-4782 1982

Adult T-cell leukemia virus (ATLV) or ATLV-associated antigen (ATLA)-positive cell clones were isolated from peripheral blood lymphocytes of all five anti-ATLA-seropositive healthy adults tested by a limiting-dilution culture method in the presence of T-cell growth factor (TCGF) but from none of six seronegative adults similarly tested. Although ATLA-positive cells were not always detected in mass cultures of the seropositive lymphocytes, they were found consistently in T-cell cloned cultures of those lymphocytes. Continuous cultures of the ATLA-positive clones obtained were dependent on TCGF.

Five clones derives from each of the five donors were maintained for greater than 4 mo and, during culture, all of them acquired the ability to grow without added TCGF. The ATLA-positive clones formed rosettes with erythrocytes and expressed Leu 1, Leu 3a, and Leu 4 antigens but not Leu 2a antigen. These results indicate that anti-ATLA-seropositive healthy individuals carry ATLV in T cells circulating in their peripheral blood. (Author abstract) (12 Refs)

7. ZOSTER IN CHILDREN WITH CANCER: IMMUNOPRECIPITATION PROFILES (MEETING ABSTRACT).

Grose C
Department of Pediatrics, University of Texas Health Science Center, San Antonio, TX
Pediatr Res; 16(4,part2):241A 1982

Twenty children with cancer who developed zoster were enrolled in a long-term study of their humoral response to varicella-zoster virus (VZV) antigens. The immunoprecipitation profiles of acute zoster sera were easily distinguished and very similar to those of high titer VZV xenoantisera; they contained a mean of 16 polypeptides, which ranged in mol wt from 32 to much greater than 200 kilodaltons (kd) and included the major VZV capsid polypeptide (155 kd), three major glycoprotiens (118, 98 and 62 kd), actin (45 kd) and a low mol wt polypeptide. In comparison with post-zoster sera, pre-zoster sera were selectively deficient in precipitating two higher mol wt polypeptides (145 kd and 174 kd), one smaller polypeptide (32 kd), and all 3 major VZV glycoproteins. Longitudinal analyses detected elevated human antibodies to VZV-specific glycoprotein antigens up to one year after zoster, while the humoral response as measured against non-glycosylated determinants fell within a few months. Occasional reappearance of the characteristic 'zoster profile' in sera drawn during late convalescence presumably represented subclinical VZV reactivation. In summary, radioimmune precipitation is a sensitive technique by which to characterize the humoral immune response to individual VZV-specific polypeptides. (no Refs)

8. ANALYSIS OF THE EPITHELIAL AND LYMPHOID CELLS IN NASOPHARYNGEAL CARCINOMA BIOPSIES USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Iliescu V, Crawford DH, De The GB, Ellouz R
Imperial Cancer Research Fund, London, WC1E 6JJ, England
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

Anaplastic nasopharyngeal carcinoma (NPC) is a geographically restricted tumor which occurs most commonly in Southern China and in certain areas of North Africa. The tumor usually arises in the Fossa of Rosenmuller and metastasizes early to the cervical lymph nodes. Complete surgical removal is often impossible and so treatment is usually by radiotherapy. NPC is etiologically associated with Epstein Barr virus (EBV) and the malignant epithelial cells express the EB viral nuclear antigen (EBNA). The tumor tissue is heavily infiltrated with lymphocytes which have been shown to be of both B and T cell types. The B cells secrete IgA antibodies directed against the EB viral capsid and these antibodies can be found in the saliva of most NPC patients. In the present study we have used monoclonal antibodies to T and B cell subsets to further define the infiltrating lymphocyte populations. We have used double staining techniques with rhodamine and fluoresein-labelled antibodies to stain the malignant epithelial cells for EBNA and the various lymphocyte subpopulations on the same sections in order to visualize the inter-relationships between these cells. The results will be discussed in relation to the probable immunological events occurring within these tumors. (no Refs)

9. HERPES SIMPLEX VIRUS AND CANCER.

Lehtinen M, Lehtinen T, Leinikki P
Biomedical Inst., Univ. Tampere, PL 607, 33101 Tampere 10, Finland
Duodecim; 98(9):664-673 1982

Herpes simplex virus (HSV) has been a suspected cause of cancer for a long time, and especially for cervical cancer. It has never been clear whether HSV is the 'driver' or the 'passenger.' The literature on this subject is discussed in detail under six headings: epidemiological correlation, tumor-specific antigens, malignancy-inducing capacity of HSV in cells, presence of HSV in tissue samples, animal experiments, and prevention. (61 Refs) (In FIN)

10. NASOPHARYNGEAL CARCINOMA AND CERVICAL CARCINOMA IN TAIWAN, CHINA.

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Excerpta Med Int Congr Ser; 571:398-407 1982

Some epidemiological studies on nasopharyngeal cancer (NPC) and cervical cancer (CC) in Taiwan are presented; possible association with oncogenic viruses is also discussed. Epidemiological data presented are based on surveys since neoplasms are not reportable in Taiwan. The age-standardized death rate (per 100,000 of population) for NPC in 1979 was 3.3 (4.6 for males, 1.9 for females). As in other countries, the rate was higher in the Chinese population. The death rate has increased slightly during the past 15 yr. Morbidity incidence from 1969-1971 of NPC was estimated at 5.4. Patients with NPC show a significantly higher anti-virus capsid antigen (VCA) titer than neighborhood controls, their families, and NPC family members. A synergistic interaction with NPC was found between all pairs of factors of smoking, ventilation, nasal balsam or oil, herb drugs, and anti-VCA titer, except that between herb drugs and ventilation. The age standardized death rate (per 100,000 of female population) for CC in 1979 was 6.9, which ranked CC fourth among causes of death in females. The death rate due to CC increased markedly after age 40 yr. CC death rates were higher in those who were ever married, compared with those who were single, widowed, or divorced. (6 Refs)

11. SEROLOGIC TESTS FOR NASOPHARYNGEAL CARCINOMA IN NORTH AMERICAN PATIENTS.

Neel HB, Pearson GR, Weiland LH, Taylor WF
Mayo Clinic and Foundation, Rochester, MN
Excerpta Med Int Congr Ser; 582:111-114 1982

The clinical value of serum titers of various Epstein-Barr virus (EBV) related antibodies was investigated in 92 North American patients with primary nasopharyngeal carcinoma (NPC), 149 patients with head and neck cancer (HNC) other than nasopharyngeal, 342 patients with benign diseases (BD) commonly seen in large otolaryngologic practices, and 100 healthy blood donors. Antibody titers of sera from patients with untreated NPC differed significantly from those of the other groups. Positive titers for the IgA anti-viral capsid antigen were found in 70% of NPC patients, only 5% of those with HNC, and 10% of those with BD. Undifferentiated and nonkeratinizing carcinomas consistently exhibited elevated antibody titers directed against viral capsid antigen and early anti-

gen. The incidence of elevated titers was lower in patients with keratinizing squamous cell carcinoma compared with the other groups. The incidence of positive IgA anti-viral capsid antigen titers in undifferentiated and nonkeratinizing varieties were much greater than those in keratinizing squamous cell varieties. A trend toward higher antibody titers with the development of metastases was seen. Of the 13 patients who died, 8 had low antibody-dependent cellular cytotoxicity titers at diagnosis and 4 had high titers. In general, patients with very high antibody-dependent cellular cytotoxicity titers remained free of disease for as long as 4 yr; these patients should be followed closely in order to determine the prognostic value of the EBV markers. (5 Refs)

12. A PRELIMINARY STUDY ON THE ANTI-EBV-SPECIFIC DNASE ACTIVITIES OF NASOPHARYNGEAL CARCINOMA (NPC) PATIENTS' SERA.

Pan Q, Huang D, Luo W, Jiao X, Chen J, Chen L
Cancer Inst., Zhongshan Medical Coll., Dongfeng Road IV, Guangzhou, People's Republic of China
Excerpta Med Int Congr Ser; 571:418-422 1982

An anti-DNase activity was demonstrated in the sera of patients in various stages of nasopharyngeal cancer (NPC). A combination of n-butyric acid (4 milliM) and croton oil (400 nanog/ml) was used to induce Epstein-Barr virus (EBV)-specific DNase in EBV-genome-containing cell lines Raji and PeHR-1. An assay utilizing 14C-DNA was devised to determine the effect of NPC patients' sera on the DNase activity of the cell homogenate. Because of the presence of an antibody in the sera of NPC patients, and the neutralizing effect of this antibody to the enzyme, addition of patients' sera markedly decreased the DNase activities to give anti-enzyme rates of 52-55%. The level of serum anti-enzyme activity varied from NPC patient to patient. There appeared to be a good parallelism between the anti-enzyme activity of the serum and its titer to viral capsid antigen to IgA. Further studies are in progress to confirm the practical value of this enzymological test for early detection of NPC. (5 Refs)

13. GENITAL HERPES AND CANCER.

Pelisse M
Service du Dr Jean Hewitt, Clinique Tarnier, 89, rue d'Assas, Paris, France
Gaz Med Fr; 89(22):2611-2612,2614 1982

Several international studies have pointed to genital herpes as a factor in the development of uterine cancer. Studies have shown that there are 2x more cases of dysplasia and 8x more uterine cancer in women with genital herpetic lesions than in a non-infected population. Cervical cellular anomalies have been detected at the end of 6 yr of surveillance following herpetic infection. Serological studies have demonstrated that 36% of the women who later developed a cancer in situ of the uterus had positive serology for herpes simplex virus. Herpetic antigens have been found in cancer cells and in dysplastic cells of the uterus. Animal studies have revealed that preparations of the virus inactivated by uv light can transform cells and then the transformed cells into tumors. Other factors such as patient age at first pregnancy, the number of pregnancies or other genital infections affect the incidence of infection with herpes simplex. Cancer of the vulva has also been associated with herpes simplex virus infections. Antigens of the virus have been found in the tumor cells of patients with cancer of the vulva. (11 Refs) (In FRE)

14. RAPID DIAGNOSIS OF VIRUS INFECTIONS IN CHILDREN ON THERAPY FOR MALIGNANCIES (MEETING ABSTRACT).

Wood DJ, Corbitt G
Booth Hall Hospital, Manchester, England
Second International Symposium on Infections in the Immunocompromised Host, June 20-24, 1982 Stirling, Scotland The Upjohn Company; :A121 1982

Patients with malignancies (mainly acute lymphoblastic leukemia) attending a Regional Pediatric Oncology Unit have been thoroughly investigated for a viral etiology by appropriate virus isolation and serological tests when presenting with a possible infection. To date, 98 virus infections have been documented with virus isolation proving more sensitive than serology. Forty-six of ninety-eight (47%) of the virus infections documented have been caused by viruses commonly associated with problems in the immunosuppressed pediatric patient (Herpesvirus hominis, Herpesvirus varicellae, cytomegalovirus and measles-virus). The remainder have been associated with commonly occurring childhood viruses, and serious, sometimes life-threatening, infections have been seen with agents such as adenoviruses, respiratory syncytial virus, parainfluenza and influenza viruses, and mumpsvirus. On the basis of these results, rapid diagnostic tests, chiefly immunofluorescence of nasopharyngeal aspirates, but also electron microscopy of body fluids, have been introduced for many of the virus antigens. The performance of the rapid tests have been monitored in parallel with the standard techniques. Attempts have also been made to assess the value of the rapid tests developed in various clinical situations. Thus, the techniques developed have been shown to be capable of rapidly detecting the majority of virus infections involving the respiratory tract and skin or mucous membranes, but not those from children with pyrexia without an obvious focus of infection, although virus infection has been documented in 20% of such cases. (no Refs)

15. SEROLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA AND CERVICAL CANCER IN CHINA.

Zeng Y
Inst. Virology, Chinese Acad. Medical Sciences, 100 Ying Xing Jie, Xuan Wu Qu, Beijing, 100052, People's Republic of China
Excerpta Med Int Congr Ser; 571:380-388 1982

A serological study on Epstein-Barr virus (EBV) infection was performed in areas of high and low risk for nasopharyngeal cancer (NPC). A micro-complement fixation test for antibody to EBV in sera of 2,300 normal individuals of all ages indicated a positive reaction in 90-100% of children aged 3-5 yr. The geometric mean titer (GMT) from the healthy population over age 20 was significantly higher in areas of high NPC risk. This type of variation may reflect reactivation of EBV in people living in the NPC high risk area and which might be related to the occurrence of NPC. Results of serologic mass surveys of NPC are reported in Zangwu county in 1978-1980. The incidence of antibody to herpes simplex virus (HSV) 1 and 2 was determined in normal women in both a high- (Jienan county) and a low-risk (Beijing) area for cervical cancer and in patients. There was no marked difference in frequency of antibody to HSV-1 in the cervical cancer patients and in the controls from high and low risk areas. However, in the cervical cancer group, the GMT of antibody to HSV-1 was a little higher than that in the control group; this may be due to cross-reaction to antigen between HSV-1 and HSV-2. A study of age-specific incidence of HSV infection in areas of high and low cervical cancer risk indicates a relationship between early and severe infection of HSV-2 and high risk of cervical cancer.

While the age-specific incidence of HSV-2 infection in China is similar to that in some western countries, the social system and life-style are quite different, indicating some other mode of infection than venereal transmission. (22 Refs)

16. THE RELATIONSHIP BETWEEN HEPATITIS B ANTIGEN AND PRIMARY LIVER CANCER.

Zhang F
Anti-epidemic Station, Manning District, Guarjxi Province, Nanning, People's Republic of China
Zhonghua Liuxingbingxue Zazhi; 3(1):49-52 1982

Two villages, S and Y, only 1,800 feet apart were investigated to determine why they showed a drastically different incidence of primary hepatoma. S had an incidence of 328.73 per 100,000 persons, whereas Y had none in 15 years. The incidence had a remarkable familial aggregation phenomena. Among 20 persons who died, 15 were from 7 families with the remaining 5 also being related to the 7 families. Natural conditions of the villages, living conditions, customs, cultures, and foods consumed were very similar in both villages. No significant differences were found in the content of aflatoxin B1 in the food of both villages. A significantly different distribution of hepatitis B-related events was found. The number of hepatitis B antigen carriers in S was clearly higher than that in Y (p less than 0.05), and more people in S than in Y had a high level of anti-hepatitis B antibody (p less than 0.001). explaining why hepatitis B viral infection rate was greatly higher in S than in Y. The rate of enlarged liver and the rate of viral hepatitis (70% were hepatitis B) were higher in S than in Y. However, no significant differences were seen between the two villages in the rate of liver function abnormality, which was found to be 42.8% for S and 51.12% for Y. Further investigation is needed to clarify these findings, which support the assumption that the hepatitis B antigen is closely related to the incidence of hepatoma. (7 Refs) (In CHI)

CHARACTERIZATION OF DNA VIRUS-ASSOCIATED ANTIGENS

17. REQUIREMENTS FOR EXCISION AND AMPLIFICATION OF INTEGRATED VIRAL DNA MOLECULES IN POLYOMA VIRUS-TRANSFORMED CELLS.

Colantuoni V, Dailey L, Valle GD, Basilico C
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J Virol; 43(2):617-628 1982

The integration of polyoma virus DNA into the genome of transformed rat cells generally takes place in a tandem head-to-tail arrangement. A functional viral large tumor antigen (T-Ag) renders this structure unstable, as manifested by free DNA production and excision or amplification of the integrated viral DNA. All of these phenomena involve the mobilization of precise genomic 'units,' suggesting that they result from intramolecular homologous recombination events occurring in the repeated viral DNA sequences within the integrated structures. We studied polyoma ts-a-transformed rat cell lines, which produced large T-Ag but contained less than a single copy of integrated viral DNA. In all of these lines, reversion to a normal phenotype (indicative of excision) was extremely low and independent of the presence of a functional large T-ag. The revertants were either phenotypic or had undergone variable rearrangements of the integrated sequences that seemed to involve flanking host DNA. In two of these cell lines (ts-a 4A and ts-a 3B), we could not detect any evidence of amplication even after 2 mo of propagation under conditions permissive for large T-Ag. An amplification event was detected in a small subpopulation of the ts-a R5-1 line after 2 mo of growth at 33 C. None of these lines spontaneously produced free viral DNA, but after fusion with 3T3 mouse fibroblasts, R5-1 and 4A produced a low level of heterogeneous free DNA molecules, which contained both viral and flanking host DNA. In contrast, the ts-a 9 cell line underwent a high rate of excision or amplification when propagated at temperatures permissive for large T-Ag function. These results indicate that the high rate of excision and amplification of integrated viral genomes observed in polyoma-transformed rat cells requires the presence of regions of homology (ie, repeats) in the integrated viral sequences. Therefore, these events occur via homologous intramolecular recombination, which is promoted directly or indirectly by the large viral T-Ag. (28 Refs)

18. AN EXAMINATION OF ADENOVIRUS TYPE 5 MUTANTS FOR THEIR ABILITY TO INDUCE GROUP C ADENOVIRUS TUMOR-SPECIFIC TRANSPLANTATION ANTIGENICITY IN RATS.

Gallimore PH, Williams J
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Virology; 120(1):146-156 1982

The expression of Group C adenovirus tumor-specific transplantation antigenicity (TSTA) has been examined in rats using a variety of Type 5 adenovirus (Ad-5) mutants. Transformation-defective Group I E1A mutants (other than Ad-5 hr1 and hr2), Group II E1B mutants, and N gene mutants, produced significantgly lower TSTA or no TSTA when compared with levels of TSTA induced by Ad-2 and Ad-5 wild-type viruses. Two mutants, Ad-5 sub304 and Ad-5 tsf25, neither of which possess lesions within the transforming sequences, induced high levels of TSTA in vivo. (Author abstract) (43 Refs)

19. INTEGRATION AND EXPRESSION OF A TRUNCATED SIMIAN VIRUS 40 EARLY GENE FRAGMENT IN MAMMALIAN CELLS.

Horst J, Weckler C, Jacob E, Aulehla-Scholz C, Deppert W
Abteilung Humangenetik, Universitat Ulm, 79 Ulm, W. Germany
Proc Natl Acad Sci USA; 79(15):4645-4649 1982

The recombinant plasmid p102 based on pBR322 carrying approx 50% of the replicator proximal early region of simian virus 40 (SV40) DNA, including the viral origin of replication, has been constructed. It lacks a major part of the large tumor (T) antigen 3'-coding region, the T-antigen termination codon, and the polyadenylylation site. The plasmid was transferred together with the herpes simplex virus thymidine kinase (TK) gene as a selectable marker to mouse LTK- cells. TK+ cell clones were isolated and their high mol wt DNAs were shown by DNA blotting and hybridization experiments to contain the SV40 DNA fragment from the recombinant. In some of these clones, heterogeneous expression of the SV40 DNA fragment could be detected by immunofluorescence while, in control experiments in which a plasmid containing the complete SV40 early DNA region was used, this extensive heterogeneity of T-antigen expression was not observed. RNA-DNA hybridization experiments showed that the SV40-specific RNA of those clones is polyadenylylated. The mol wt of the T-antigen-related protein coded by p102 corresponded well to the expected

coding capacity of the SV40 DNA fragment. Small tumor antigen was not expressed. (Author abstract) (34 Refs)

20. P105, AN EBV-INDUCED TARGET OF THE IMMUNE RESPONSE (MEETING ABSTRACT).

Jones W, Casareale D, Reisert PS, Spiro RC, Saireuji T, Humphreys RE
University of Massachusetts Medical School, Worcester, MA, 01605
Fed Proc; 41(3):803 1982

In order to characterize EBV-induced targets of the immune response, a 105 dalton glycoprotein prominently recognized in immunoprecipitates of, Burkitt's lymphoma patients' sera with P3HR-1 EBV-superinfected Raji cells (S-Raji), was analyzed through the use of a specific heteroantiserum. Synthesis of p105 was restricted to EBV-superinfection and was not blocked with phosphonoacetic acid, indicating p105 to be an 'early' viral antigen. An external exposure of p105 on the cell surface was indicated by its glycosylation with radiolabeled sugars, by antibody binding in a radioimmunoassay with living cells and by membrane immunofluorescence. Although anti-p105 serum did not neutralize P3HR-1 virus (but bound to P3HR-1 cell membranes), it mediated antibody-dependent cellular cytotoxicity (ADCC) to EBV-superinfected Raji and to control Raji cells but not to several EBV genome-negative cell lines. We conclude that p105 is an EBV-induced, external, glycosylated, early membrane antigen to which EBV-infected patients generate a substantial antibody response. These antibodies do not neutralize infectious virus but might mediate ADCC to, or otherwise affect, infected cells early in the virus cycle. (no Refs)

21. TWO DIFFERENT VIRAL TRANSFORMING PROTEINS BIND THE SAME HOST TUMOUR ANTIGEN.

Lane D, Harlow E
Eukaryotic Molecular Genetics Group, Imperial Coll. Sciences and Technology, London SW7 2AZ, England
Nature; 298(5874):517 1982

The implications of the discovery of proteins produced by two DNA tumor viruses that are able to complex p53 are discussed in relation to the immunogenicity of p53 in animals with cancer. In mouse cells, p53 becomes tightly associated with a 58,000-mol wt product of the adenovirus E1b region. In Simian virus 40-transformed mouse cells, p53 also binds to the Simian virus 40-coded large T antigen. Levels of p53 are high in transformed cells are higher than in normal cells. (13 Refs)

22. EVIDENCE FOR NON-CHROMOSOMAL HEPATITIS B VIRUS SURFACE (HBSAG)- AND CORE ANTIGEN (HBCAG)-SPECIFIC DNA SEQUENCES IN A HEPATOMA CELL LINE.

Marquardt O, Zaslavsky V, Hofschneider PH
Max-Planck-Institut fur Biochemie, 8033 Martinsried, W. Germany
J Gen Virol; 61(part1):105-109 1982

As demonstrated previously, a 'beta particle' fraction isolated from the cytoplasm of PLC/PRF/5 cells contains hepatitis B virus (HBV)-specific DNA. Here, further evidence is provided that the specificity of the DNA for HBV is represented at least by sequences coding for the surface and core antigen (HBsAg and HBcAg). This was shown by two different hybridization techniques. One of them, the technique of Southern, distinguished these hybrid molecules formed from those containing HBV DNA integrated into chromosomes. The HBV-specific beta particle DNA forms two distinct bands separate from the high mol wt cellular DNA. (Author abstract) (13 Refs)

23. THE BINDING OF SIMIAN VIRUS 40 LARGE T ANTIGEN TO THE POLYPHOSPHATE BACKBONE OF NUCLEIC ACIDS.

Montenarh M, Henning R
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Biochim Biophys Acta; 697(3):322-329 1982

Simian virus 40 (SV40) large tumor antigen (T antigen), a phosphoprotein found in nuclei of SV40-infected and -transformed cells, binds nonspecifically to DNA. To study this mechanism the binding properties of T antigen to double-stranded (ds) and single-stranded (ss) DNA-cellulose as well as to phosphocellulose were compared. After incubation of [35S]methionine or [3H]leucine/[32P]phosphate radioactively-labeled cell extracts at different pH values (6.0, 7.3, 9.0) with DNA- or phosphocellulose, bound and unbound species of T antigen were purified and analyzed by SDS-polyacrylamide gel electrophoresis for both the yield and the possible correlation with protein phosphorylation. T antigens bound with comparable affinities to ds- and ss-DNA-cellulose and phosphocellulose. These results suggest the binding of T antigen to the polyphosphate backbone of DNA as a molecular mechanism for its nonspecific binding. The evidence for this observation was supported by blocking the binding of T antigen to DNA-cellulose by divalent cations (Ca++, Mg++). 3H/32P ratios of T antigen obtained by double-labeling cells for various times imply that higher phosphorylated forms of T antigen bound more strongly to ds- and ss-DNA as well as to phosphocellulose. Thus, in the presence of cellular proteins and other components the binding activity of T antigen to the polyphosphate backbone of DNA seems to be positively correlated with its phosphorylation. These observations are consistent with the hypothesis that the binding affinities of SV40 T antigen to host cell DNA may be regulated by its phosphorylation. (Author abstract) (24 Refs)

24. CONSTRUCTION AND CHARACTERIZATION OF VIABLE DELETION MUTANTS OF SIMIAN VIRUS 40 LACKING SEQUENCES NEAR THE 3' END OF THE EARLY REGION.

Polvino-Bodnar M, Cole CN
Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Virol; 43(2):489-502 1982

Five viable deletion mutants of simian virus 40 (SV40) were prepared and characterized. These mutants lack 15 to 60 base pairs between map positions 0.198 and 0.218, near the 3' end of the early region of SV40 and extend further into the body of the A gene, encoding the large T antigen, than previously described deletion mutants. These mutants were isolated after transfection of monkey kidney CV-1p cells with full-sized linear DNA prepared by partial digestion of form I SV40 DNA with restriction endonucleases HinfI or MboII, followed by removal of approximately 25 base pairs of DNA from the 5' termini using gamma-5'-exonuclease and purification of the DNA in agarose gels. Based on comparisons of the DNA sequence of SV40 and polyoma virus, these mutations map in the 19% of the SV40 A gene that shares no homology with the A gene of polyoma virus. The mutations exist in two different genetic backgrounds: the original set of mutants (dl2401 through dl2405) was prepared, using as a parent SV40 mutant dl862, which has a deletion at the single HpaII site (0.725 map unit). A second set (dl2491 through dl2495) contains the same deletions in a wild-type SV40 (strain SV-S) background. Relative to wild-type SV40, the original mutants showed reduced rates

of growth, lower yields of progeny virus and viral DNA, and smaller plaque size; in these properties the mutants resembled parental dl862, although mutant progeny yields were usually lower than yields of dl862, suggesting a possible interaction between the two deletions. The second set of mutants had growth properties and progeny yields similar to those of wild-type SV40; however, Southern blotting experiments indicated that viral DNA replication proceeds at a slightly reduced rate. All of the mutants transformed mouse NIH/3T3 cells and mouse embryo fibroblasts at the same frequency as wild-type SV40. Mutants dl2402, dl2492, and dl2405 consistently produced denser and larger foci in both types of cells. All mutants directed the synthesis of shortened large T antigens. Adenovirus helper function was retained by all mutants. (Author abstract) (83 Refs)

25. PURIFICATION AND BIOLOGIC CHARACTERIZATION OF A MAJOR EPSTEIN BARR VIRUS-INDUCED MEMBRANE GLYCOPROTEIN.

Qualtiere LF, Chase R, Pearson GR
Dept. Microbiology, Univ. Saskatchewan, Saskatoon, Saskatchewan, S74 0W0, Canada
J Immunol; 129(2):814-818 1982

The Epstein Barr virus membrane antigen (MA) complex is composed of three major high mw glycoproteins designated gp 300/350, gp 200/250, and gp 85/90. In the experiments reported in this paper, the gp 300/350 glycoprotein was purified from MA-positive extracts prepared from the B-95-8 cell line. This was accomplished by tandem combination of ion-exchange and lectin chromatography. It was routinely possible to purify this glycoprotein 400-600-fold by this procedure. Sera from animals immunized with gp 300/350 purified by this approach neutralized EBV infectivity and mediated antibody-dependent cellular cytotoxicity (ADCC) demonstrating that both of these important antigenic determinants were expressed on this glycoprotein. The presence of an ADCC determinant on this molecule was further substantiated by the finding that monoclonal antibody to gp 300/350 blocked ADCC mediated by a human ADCC antibody-positive reference serum. (Author abstract) (27 Refs)

26. CHARACTERIZATION OF AN ANTIGEN ASSOCIATED WITH THE MAREK'S DISEASE LYMPHOBLASTOID CELL LINE MSB-1.

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J Gen Virol; 60(part2):375-380 1982

A Marek's disease lymphoblastoid cell line (MSB-1) has been analyzed by immunoprecipitation for expression of tumor-associated antigen, Marek's disease virus (MDV)-specific antigens and antigens specific to avian leukosis-sarcoma viruses. Rabbit antisera raised against two independently derived cell lines after extensive absorption with normal chick cells reacted with a polypeptide of mol wt 40,000 (40K) in extracts of MSB-1 cells. The 40K polypeptide was not present in myeloblasts or in chick embryo fibroblasts (CEF) infected with MDV and did not react with antiserum raised against normal chicken thymus antigens. The possibility that the 40K polypeptide is a tumor-associated antigen is discussed. Seven MDV-specific antigens were noted in infected CEF (mol wt 110K, 100K, 80K, 70K, 50K, 35K and 32K) but none of these was detected in MSB-1 cells. The avian leukosis-sarcoma group-specific antigen P27gag and its precursor Pr76gag were not found in MSB-1 cells, confirming that expression of mature gag protein is not required for transformation by MDV. However, two polypeptides of unknown origin and function (mol wt 180K and 110K) were precipitated from MSB-1 cells with a rabbit anti-Rous sarcoma (Schmidt-Rupin, subgroup D) antiserum. (Author abstract) (17 Refs)

27. A MONOCLONAL ANTIBODY DETECTING THE ADENOVIRUS TYPE 5 E 1B-58KD TUMOR ANTIGEN: CHARACTERIZATION OF THE E 1B-58KD TUMOR ANTIGEN IN ADENOVIRUS-INFECTED AND -TRANSFORMED CELLS.

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Virology; 120(2):510-517 1982

A monoclonal antibody directed against the adenovirus Type 5 E1b-58Kd tumor antigen has been isolated. Immune clearing experiments were employed to demonstrate that this monoclonal antibody detects the same E1b-58Kd antigen observed previously with polyclonal antisera from hamsters bearing adenovirus-induced tumors. Fluorescent antibody tests using the monoclonal antibodies directed against the E1b-58Kd antigen localized the viral protein predominantly in the nucleus of virus-infected and -transformed cells. The monoclonal and polyclonal tumor sera detected similar protein species in virus-infected and -transformed cells. In adenovirus productively infected human cells the monoclonal antibody and polyclonal tumor sera both detected a 25K protein in addition to the E1b-58Kd antigen. In transformed mouse and hamster cells this monoclonal and polyclonal antisera coimmunoprecipitated a 53Kd cellular protein along with the E1b-58Kd antigen. This 53Kd cellular protein is similar to the p53 antigens detected in a variety of transformed cells. (Author abstract) (25 Refs)

28. AUGMENTED IMMUNOGENICITY OF LEWIS LUNG CARCINOMA BY INFECTION WITH HERPES SIMPLEX VIRUS TYPE 2.

Reiss-Gutfreund RJ, Nowotny NR, Dostal V, Wrba H
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Eur J Cancer Clin Oncol; 18(6):523-531 1982

In vitro, LLT cells sustain HSV-2 replication without evidence of lysis. Simultaneously, multiplication of the cells is stimulated. These xenogenized cells were tested for their immunopotentiating capacity: three-step immunization with xenogenized viable cells conferred significantly augmented transplantation resistance to a challenge graft with 4 x 10(4) intact LLT cells. Latency periods preceding tumor formation were increased and 15% of the mice failed to form primary tumors. Metastasis was likewise decreased and 25% of the mice had healthy lungs. Immunopotentiation, however, did not suffice to significantly protect against a challenge with 6 x 10(4) intact cells. The presence of virus-specific neoantigens on HSV-2-infected viable cells was demonstrated by the progressively increasing number of rejections of 4 x 10(4) xenogenized cells during the successive immunization steps. Immunization with non-viable LLT cells did not augment resistance to challenge. (Author abstract) (31 Refs)

29. A NOVEL CELL TRANSFORMATION WITH DNA-CONTAINING CYTOPLASMIC YABA TUMOR POXVIRUS.

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Virology; 120(1):77-92 1982

Monkey kidney cells were morphologically transformed in vitro with uv-irradiated Yaba tumor poxvirus. Cell lines established were shown to be virus nonproducers and exhibited biological characteristics typical of transformed cells. These characteristics included increased saturation density, reduced serum requirements for growth, and ability to grow in soft agar. The morphological alterations of transformed cells were similar to Yaba virus-induced tumor cells and were characterized by loss of contact inhibition, multinucleated cells, and cytoplasmic lipid droplets. Southern blot hybridization revealed that sequences homologous to low-mol-wt viral DNA were present in the transformed cells. Yaba virus-specific antigens detected by immunofluorescence assays were found to be in the cytoplasm of transformed cells. Four virus-specific proteins, with mol wt of 160,000, 140,000 107,000, and 74,000 daltons, were detected in transformed cells immunoprecipitated with sera from tumor-bearing monkeys. These results indicate that DNA-containing Yaba tumor virus, which replicates exclusively in the cytoplasm, is capable of inducing cell transformation in vitro. (Author abstract) (32 Refs)

30. STIMULATION OF HOST CENTRIOLAR ANTIGEN IN TC7 CELLS BY SIMIAN VIRUS 40: REQUIREMENT FOR RNA AND PROTEIN SYNTHESES AND AN INTACT SIMIAN VIRUS 40 SMALL-T GENE FUNCTION.

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J Virol; 43(2):721-729 1982

Simian virus 40 (SV40) stimulated a host cell antigen in the centriolar region after infection of African green monkey kidney (AGMK) cells. The addition of puromycin and actinomycin D to cells infected with SV40 within 5 hr after infection inhibited the stimulation of the host cell antigen, indicating that de novo protein and RNA syntheses that occurred within the first 5 hr after infection were essential for the stimulation. Early viable deletion mutants of SV40 with deletions mapping between 0.54 and 0.59 map units on the SV40 genome, dl2000, dl2001, dl2003, dl2004, dl2005, dl2006, and dl2007, did not stimulate the centriolar antigen above the level of uninfected cells. This indicated that an intact, functional small-t protein was essential for the SV40-mediated stimulation of the host cell antigen. Our studies, using cells infected with nondefective adenovirus-SV40 hybrid viruses that lack the small-t gene region of SV40 (Ad2+ND1, Ad2+ND2, Ad2+ND3, Ad2+ND4, and Ad2+ND5), revealed that the lack of small-t gene function of SV40 could be complemented by a gene function of the adenovirus-SV40 hybrid viruses for the centriolar antigen stimulation. Thus, adenovirus 2 has a gene(s) that is analogous to the small-t gene of SV40 for the stimulation of the host cell antigen in AGMK cells. (Author abstract) (57 Refs)

31. EVIDENCE FOR TWO CLASSES OF CHROMATIN-ASSOCIATED EPSTEIN-BARR VIRUS-DETERMINED NUCLEAR ANTIGEN.

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J Virol; 43(2):555-565 1982

A new class of Epstein-Barr virus nuclear antigen (EBNA) was identified by the complement fixation assay. This new species of EBNA is more tightly bound to chromatin and was termed Class II EBNA, as opposed to the more weakly associated species, Class I EBNA. Preparations of this new antigen(s) specifically reduced absorption with the titer of anti-EBNA antibodies as determined by the anticomplement immunofluorescence assay. Therefore, the complement fixation antigens (Class II EBNA) appear to be related to the classical EBNA (Class I EBNA). The Class I EBNA was found to focus at the same pH (4.6) as the soluble antigen found in the cytosol. The Class II EBNA differed from the Class I EBNA with regard to its overall charge, molecular size, antigenicity, and affinity for chromatin. The Class II EBNA appeared to be a basic protein, based on its apparent pI of 9.2 and its binding to cation-exchange resins. It differed from histones with regard to its molecular size (mol wt between 60,000 and 70,000) and its elution from hydroxylapatite chromatography. Steps were taken to prevent proteolysis and artifacts in the immunological assays and in the overall charge estimation of the new antigen by nonspecific basic histone protein-acidic protein interactions. Both Class I and Class II EBNA were identified by radioimmunoelectrophoresis on two-dimensional polyacrylamide gels with pI values of 5.0 and 8.5, respectively, and a mol wt range of 60,000 to 70,000 for both. A lower-mol-wt antigen identified by molecular sieve chromatography appeared to be due to interference by histones in the immunoassays since it was not observed by the two-dimensional gel electrophoresis. Further characterization of this Class II EBNA is in progress. (Author abstract) (40 Refs)

32. IMMUNOCHEMICAL CHARACTERIZATION OF EBV ANTIGENS DETECTED BY DOUBLE IMMUNODIFFUSION.

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Intervirology; 17(4):208-214 1982

Double immunodiffusion (Ouchterlony) tests gave regularly positive reactions when extracts of [35S]-methionine-labeled, n-butyrate-induced P3HR-1 cells were allowed to react with serum pools with high Epstein-Barr virus (EBV) antibody titers from Burkitt lymphoma or nasopharyngeal carcinoma patients, but not with EBV antibody-negative sera. Similarly prepared extracts of noninduced P3HR-1 cells gave no precipitation lines with the antibody-positive sera. The composition of the precipitates was analyzed by SDS-PAGE and compared with immunoprecipitates obtained by indirect immunoprecipitation in soln. Three lines precipitated on the Ouchterlony plate were analyzed; these lines were located at close (a), intermediate (b), and distant (c) positions in relation to the antigen well. Precipitate (a) contained polypeptides with mol wt of 165,000 (165K), 152K, 138K, 134K, 103K, and 55K. Precipitate (b) contained 152K and 138K as the major components, while 55K was relatively underrepresented. Precipitate (c) contained 90K and 55K as major components, while 152K was a minor component. The method is suitable for the study of possible subtype differences between defined antigenic com-

ponents of the early and late EBV-determined antigen complexes. (Author abstract) (9 Refs)

33. MALIGNANT RABBIT FIBROMA VIRUS: REPORT OF A NEW VIRUS-INDUCED TUMOR CAUSING SECONDARY IMMUNODEFICIENCY (MEETING ABSTRACT).

Strayer DS, Corbeil LB, Cabirac G, Leibowitz J, Skaletsky E, Sell S
University of California, San Diego, La Jolla, CA, 92093
Fed Proc; 41(3):408 1982

Shope fibroma virus (SFV) causes a local, transient proliferation of fibroblasts, which peaks in 10 days and quickly regresses. We have isolated and identified another DNA poxvirus derived from tumors by SFV. This virus, which we call Malignant Rabbit Fibroma Virus (MRF), is antigenically similar to SFV. Immune sera to SFV cross-neutralized MRF and SFV in vitro equally. The clinical syndrome is different: a bizarre fibroblastic proliferation develops locally, followed by histologically identical cutaneous metastases by day 6-7. Simultaneously latent colonization with Pasteurella multocida becomes purulent conjunctivitis and rhinitis. Death soon ensues from respiratory obstruction. Splenic B cell function, measured by anti-Ig blastogenesis, is depressed by day 6 compared to normals and SFV-infected rabbits. Splenic T cell function, measured by con A (concanavalin A) stimulation, and is similarly depressed. Peripheral blood lymphocyte responses are also affected. The depression in immune responsiveness is thus first apparent just before the clinically obvious metastases appear. MRF-induced tumors are possible models for secondary immunologic incompetence and gram-negative infections in oncology. (no Refs)

34. SIMPLE ASSAY METHOD FOR SUSCEPTIBILITY OF HUMAN LYMPHOCYTES TO EPSTEIN-BARR VIRUS INFECTION.

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Intervirology; 18(1/2):87-91 1982

On the basis of the sequential early events induced by Epstein-Barr virus (EBV), the infectability of human lymphocytes to EBV was quantified as a plateau value of the max nuclear antigen (EBNA) synthesis preceding cellular DNA synthesis. The frequency of EBV-infectable cells was an av of 7.6% of unfractionated umbilical cord lymphocytes and was 4.9% in the counterparts from human adults. In the B-cell-enriched populations, the av plateau values were 29.2% in umbilical cord and 15.5% in adult samples. This method is simple and applicable for quantitative assay of the sensitivity to EBV infection of a given lymphocyte preparation. (Author abstract) (18 Refs)

35. EXPRESSION OF RECEPTORS FOR EPSTEIN-BARR VIRUS (EBV) ON LYMPHOID LEUKEMIC CELLS (MEETING ABSTRACT).

Vogler LB, Lenoir M, Flandrin G, Gerber P
Laboratories of Immunochem. and Immunopath. and Cytology, Hopital St. Louis, Paris, France
Pediatr Res; 16(4,part2):217A 1982

EBV has an unique affinity for human B lymphocytes. It is associated with infectious mononucleosis, African (endemic) Burkitt's lymphoma, nasopharyngeal carcinoma, and an x-linked lymphoproliferative (Duncan's) disease. To better understand the nature of EBV receptors on B cells, we examined receptor expression on lymphoid leukemic cells representative of discrete stages of lymphocyte differentiation, using an immunofluorescent method. Cells were incubated with EBV, then FITC-F(ab')2 fragments of human IgG anti-EBV membrane antigen. We conclude that EBV receptors appear very early, at the pre-B stage, in B cell development and that they are lost at or shortly before terminal differentiation to plasma cells. Non-endemic Burkitt's cells lacked receptors for EBV, suggesting an origin of this malignancy from an unique set or developmental stage of B lymphocytes. (no Refs)

36. CHANGES IN THE EXPRESSION OF FC RECEPTOR PRODUCED BY INDUCTION OF EPSTEIN-BARR VIRUS IN LYMPHOMA CELL LINES.

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Virology; 120(2):376-382 1982

Induction of Epstein-Barr virus (EBV) in the human lymphoma lines P3HR-1, and Daudi by TPA (phorbol-12-myristate-13-acetate), n-butyrate, and superinfection with P3HR-1 virus is associated with an increase in the number of cells bearing Fc receptor (Fc-R). The number of Fc-R per cell, as measured by flow cytometry, is also increased in both cell lines after effective induction of EBV antigens. The increase in cells bearing Fc-R correlates with increased expression of the membrane antigen complex (MA). A high proportion of induced cells concomitantly express both Fc-R and MA in double fluorescence studies. Fc-R activity was not induced by these treatments in EBV-negative lines. After induction of B-95-8 cells (an EBV-transformed marmoset cell line), there is an increase both in MA and whole virus production; however, no Fc-R activity has been detected, suggesting that the B-95-8 EBV strain is incapable of inducing an Fc-R at the cell surface. (Author abstract) (20 Refs)

CHARACTERIZATION OF RNA VIRUS-ASSOCIATED ANTIGENS

37. TRANSFORMATION OF HUMAN LEUKOCYTES BY COCULTIVATION WITH AN ADULT T CELL LEUKEMIA VIRUS PRODUCER CELL LINE.

Yamamoto N, Japan, Okada M, Koyanagi Y, Kannagi M, Hinuma Y
Inst. Virus Res., Kyoto Univ., Kyoto 606
Science; 217(4561):737-739 1982

The transmission of adult T cell leukemia virus, a human retrovirus, into fresh leukocytes from normal humans was examined. One of three virus-carrying cell lines, tested after being subjected to lethal x-irradiation, consistently transformed leukocytes from adult peripheral blood and umbilical cord blood. All the transformed cell lines expressed adult T cell leukemia virus-associated antigen, but transformed lines originating from adult and umbilical cord blood exhibited T cell and non-T, non-B cell surface natures, respectively. Efforts to transform human leukocytes with cell-free virus were unsuccessful. (Author abstract) (16 Refs)

38. ANTIGENIC AND CHROMOSOMAL CHANGES IN THYMUS AND SPLEEN OF BALB/MO MICE DURING LEUKEMOGENESIS.

Asjo B, Fenyo EM, Spira J
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden
Leuk Res; 6(3):413-419 1982

Correlation between the amplification of the Moloney murine leukemia virus (M-MuLV) and appearance of M-MuLV induced cell surface antigen, MCSA, on thymus cells was studied in Balb/Mo mice. Production of infectious virus in the preleukemic mice was accompanied by the appearance of viral p30 antigen on the surface of thymus cells. All organs of Balb/Mo mice were negative for MCSA up to 40 days. Thereafter occasional thymuses contained a low fraction of MCSA-positive cells. Thus, Balb/Mo mice differed from mice neonatally inoculated with M-MuLV since the amplification of the viral genome was not accompanied by the appearance of MCSA on thymus cells. Mice mainly developed lymphomas with two distinct clinical manifestations. One type was characterized primarily by enlargement of spleen and lymph nodes, and the other by enlargement of thymus with eventual infiltration of peripheral lymphatic organs. Leukemia latency varied between 3-10 mo and was not correlated with any particular type of lymphoma. Thymus cells were often MCSA positive while spleen cells of the same animal were MCSA negative. Based on the antigen patterns of thymomas and lymphomas, Balb/Mo lymphoma mice were more often negative for MCSA (68%) than mice receiving M-MuLV at birth (40%). The majority of thymus cells was MCSA positive while the spleen was MCSA negative. No correlation between the antigen expression and chromosome constitution could be observed. Amplification of the M-MuLV genome in young Balb/c mice was not accompanied by the appearance of MCSA on thymus cells. Results suggested that MCSA is related to a virus activated in a minority of Balb/Mo mice during the late phase of leukemogenesis. (14 Refs)

39. SEROLOGICAL CHARACTERIZATION OF C-TYPE RETROVIRUSES ENDOGENOUS TO THE C57BL/6 MOUSE AND ISOLATED IN TUMOURS INDUCED BY RADIATION LEUKAEMIA VIRUS (RADLV-RS).

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J Gen Virol; 61(part1):55-63 1982

Radiation leukemia virus, Rs strain (RadLV-Rs), is a virus complex derived from radiation-induced lymphoma of the C57BL/6 mouse. Several B-ecotropic retroviruses (T1223/B, T98/B and T128/B) were isolated from the RadLV-Rs and further cloned. They were found to be highly leukemogenic and polymorphic in terms of XC cell fusion activity. To investigate a possible relationship between their phenotypical and genotypical properties, a serological characterization of their proteins was undertaken by means of interference, neutralization and type-specific radioimmunological experiments. In addition, these viruses were compared on the basis of the electrophoretic mobility of their proteins. They were also compared with the prototype endogenous N-ecotropic (BL6/Ni) and xenotropic (T530/X) retroviruses of the C57BL/6 mouse as well as the AKR-MuLV and the RadLV/VL-3 (thymotropic leukemogenic retrovirus involved in radio-induced lymphoma). With respect to the P12, T1223/B and T128/B viruses were of xenotropic type as in RadLV/VL-3, whereas T98/B p12 displayed ecotropic and xenotropic type-specific antigenic determinants. The gp71 of all B-ecotropic virus isolates were indistinguishable and of the AKR-MuLV type. This latter result was further supported by interference and neutralization experiments. This supports the view that the B-ecotropic virus isolates originated by recombination (1 or 2 events) between N-ecotropic and xenotropic endogenous retroviruses. The RadLV/VL-3 possesses a unique envelope recombinant glycoprotein of which the antigenicity was not observed in the RadLV-Rs complex. Thus, it may be assumed that the leukemogenic components of RadLV and RadLV-Rs arose by different recombinational mechanisms. (Author abstract) (29 Refs)

40. CIRCULATING IMMUNE COMPLEXES, ANTIGENS, AND ANTIBODIES RELATED TO THE MURINE MAMMARY TUMOR VIRUS IN C3H MICE.

Dong ZW, Witkin SS, Fernandes G, Sarkar NH, Good RA, Day NK (c/o Day), Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
J Immunol; 129(2):872-876 1982

A comparative study was performed to measure levels of free antibody to MuMTV, MuMTV membrane antigen (gp52), and antigen-antibody complexes in sera of mammary tumor-bearing and age-matched non-tumor bearing C3H/Bi mice. Approx 90% of these mice spontaneously develop breast cancer. Levels of MuMTV antibody and C3-containing circulating immune complexes (CIC) were highest in the sera of the mice without overt evidence of breast cancer. MuMTV gp52 antigen was present in higher concentrations in the sera of mice with overt breast cancer. Fractionation of the sera on sucrose gradients followed by analysis for CIC confirmed that levels of C-containing CIC were lower in sera from mice with tumors than in nontumor bearers. The CIC were, however, of smaller size in sera of tumor-bearing mice. When the sera were assayed for CIC by an assay in which C binding does not compete with binding of CIC to the sperm, the levels of these small-sized CIC in sera of mice with breast cancer were now comparable to CIC levels in nontumor-bearing mice. MuMTV antibody was located in both 7S and high mw regions of the gradients. To determine whether the CIC contained MuMTV antigen, the CIC were bound to bull sperm Fc receptors and assayed for reactivity with monospecific goat anti-gp521gG. Significantly higher levels of reactivity to anti-gp52 were detected in CIC from C3H mice than in CIC from sera of age-matched AKR mice with or without leukemia or from MRL/MpJ-Ipr/Ipr mice. These data indicate that there is a shift from MuMTV antibody excess to MuMTV antigen excess and from larger C-fixing CIC to smaller non-C-fixing CIC after appearance of overt breast cancer in C3H mice. (26 Refs)

41. ONCOVIRAL PROTEINS AS CELLULAR ANTIGENS.

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Curr Top Microbiol Immunol; 98:37-80 1982

The immunological recognition of proteins encoded by oncoviruses and the biological consequences of recognition are reviewed. Virally produced proteins include structural proteins of the virion, variants of these proteins that do not reside on the virions, and proteins that are coded by cellular genes that have become incorporated into the oncoviral genome. The last-mentioned type of protein can produce malignant transformation. Many viral proteins are found on the cell surface membrane and therefore act as antigens. As antigens, the proteins provide a target for immune response by the host. The immune response may be useful for in vitro serological analysis. The

murine system has provided a model for study of immune response by the host to virion structural proteins and the expression of endogenous viral proteins in various hematopoietic cell lineages. The feline system has been a model for assessment of host responses to virally-induced malignancy. The feline system has produced the best evidence that an immune response by the host to viral transformation antigens can be decisive in rejection of a tumor and indicative of the incidence of a tumor in a population. Discussion emphasizes recognition in the host species from which particular viruses were derived. Only C-type viruses are discussed. (400 Refs)

42. FUSION INJECTION OF ROUS SARCOMA VIRUS PROTEINS INTO ROUS SARCOMA VIRUS-TRANSFORMED, NON-PRODUCING HAMSTER CELLS CAUSES RELEASE OF INFECTIOUS VIRUS.

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J Gen Virol; 61(part1):83-86 1982

Purified virus proteins from transformation-defective (td) mutants of Rous sarcoma virus PrA or PrB were trapped in human erythrocyte ghosts which, after resealing, were fusion-injected into hamster RBH cells or rat TWERC cells. These cell lines are non-productively transformed by subgroup C Rous sarcoma virus. After fusion injection the hamster RBH cells released transforming subgroup C Rous sarcoma virus. No infectious virus could be rescued from rat TWERC cells. Since previous experiments have shown that fusion injection of the purified Rous sarcoma virus protein p15 into hamster RBH cells caused cleavage of the precursor protein pr76 to form the virus group-specific antigen (gag) but did not induce infectious virus, we conclude that in addition to p15 other virus proteins are required to induce virus rescue in hamster RBH cells. (Author abstract) (10 Refs)

43. BIOLOGICALLY ACTIVE COMPONENTS OF A PERCHLORIC ACID EXTRACT OF MTV-INDUCED MAMMARY TUMORS (MEETING ABSTRACT).

Laing CA, Japal KM
Howard University Cancer Center, Washington, DC, 20060
Med Pediatr Oncol; 10(1):103 1982

Spleen cells of BALB/c mice inoculated with 1x10(6) viable MTV (mammary tumor virus) induced mammary tumor cells exhibited, in vitro, a biphasic DNA synthetic response to syngeneic antigenic extracts (AMMT) of the tumor isolated by Perchloric Acid extraction. The first phase of the response peaked at 10 or 13 days post inoculation and declined drastically three days thereafter. The second phase appeared 3-6 days after the decline of the first (13-16 days post inoculation) and correlated with ulceration, infection, and central necrosis of the tumor. The response predominantly T-cell mediated. The levels of Theta (Thy 1.2) and Ig positive cells of the spleen differed only slightly from controls at intervals over the 25 day period post inoculation. Macrophage population rose from less than 2% in controls to 12% at appearance of the first peak and persisted through the decline. With ulceration of the tumor the macrophage population rose sharply to exceed 25% by day 25. When spleen cells were depleted of macrophages (so that residual macrophages constituted approximately 2% of the depleted population) and cultured with AMMT, the response was impaired (compared to undepleted cells) over the duration of the first phase. At the decline, depletion of the macrophage population further suppressed the low level of predepletion reactivity seen. At the second phase depletion of macrophages resulted in an enhancement of the response. AMMT eluted into two active fractions (MW 70,000 and 38,000) on LKB ultrogel. Specific activity of the 70,000 MW fraction was increased up to 40 fold above the crude fraction. Thus AMMT is capable of initiating lymphoproliferative response in previously sensitized cells. The response is regulated by macrophages which may exert either a supportive or suppressive role. (no Refs)

44. EXPRESSION OF XENOTROPIC MURINE LEUKEMIA VIRUSES.

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Curr Top Microbiol Immunol; 98:17-26 1982

Expression of xenotropic murine leukemia viruses (X-MuLV) and X-MuLV-encoded glycoprotein 70 (gp70) antigens was studied in various strains of mice. Genetic information from X-MuLV was found in all strains of mice; expression of this information as infectious virus or gp70 antigens was negatively controlled in most strains. In strains that express high levels of infectious MuLV, negative control was overcome in a variety of ways. Expression of infectious MuLV was not related to the strain of mouse. Expression of MuLV as infectious virus or X-MuLV-coded cell surface antigens (XenCSA) was determined by different factors. In most inbred strains of mice levels of XenCSA were controlled by genes that govern differentiation of T-lymphocytes. Expression of X-MuLV information in T-cells was not related to expression in B-cells. Crosses between inbred strains show different forms of genetic control of the expression of X-MuLV. Findings show no evidence that the products of X-MuLV genes play a role in any normal physiological process. Such a role is, however, not excluded by the evidence. (29 Refs)

45. COMPARISON OF MAMMARY TUMORIGENESIS BETWEEN LITTERS IN RELATION TO MAMMARY TUMOR VIRUS ANTIGENIC EXPRESSION IN THE MILK OF C3H/HE MICE.

Nagasawa H, Nakajima Y, Morimoto J, Imai S, Tsubura Y
Experimental Animal Res. Lab., Meiji Univ., Tama-ku, Kawasaki,, Kanagawa 214, Japan
Life Sci; 31(1):83-88 1982

As a possible step to estimate the relationship between mammary tumor virus (MTV) and mammary tumorigenesis in mice, MTV antigenic expression in mother's milk and spontaneous mammary tumorigenesis in their daughters were compared between the first, the second and the third litters of the highly inbred strains of C3H/He mice with low mammary tumor incidence. While MTV antigenic expression was detected in all undiluted samples at each litter by immunodiffusion test, the amount of antigen as measured by the single radial immunodiffusion method was increased with increasing litter numbers. On the other hand, the development of preneoplastic mammary hyperplastic alveolar nodules was different little between litters and mammary tumor incidence by 13 mo of age was very low with no difference in all litters. The pattern of estrous cycles and plasma prolactin level were also similar in each litter. The results suggest that spontaneous mammary tumorigenesis in mice is not always affected quantitatively by the amount of MTV when endocrine and genetical conditions are similar. (Author abstract) (19 Refs)

46. IDENTIFICATION AND CHARACTERIZATION OF A 200,000 DALTON TUMOR ANTIGEN OF AVIAN SARCOMA VIRUS TRANSFORMED BALB/C CELLS (MEETING ABSTRACT).

Parsons SJ, McCarley DJ, Parsons JT, Benjamin DC
University of Virginia, Charlottesville, VA, 22901
Fed Proc; 41(3):555 1982

BALB/c bearing mice tumors induced by avian sarcoma virus (ASV) produce antibodies which immunoprecipitate the viral transforming protein, pp60src, and in some cases, antibodies to phosphoproteins with Mr ranging from 110 to 250 kd. Monoclonal antibodies were produced and used to determine whether these phosphoproteins either play a role in tumor rejection or are associated with pp60src, a known kinase. One monoclonal antibody specifically immunoprecipitates a major polypeptide of 200 kd and two minor polypeptides of 18 and 15 kd. The 200 kd peptide (p200) is found in both normal and transformed mammalian cell lines and chicken embryo fibroblasts (CEF). P200 from normal CEF appears to be slightly smaller in size and either less abundant or less highly phosphorylated than its transformed counterpart. Immunoaffinity purified ASV-BALB/c extracts contain these three polypeptides which, along with several other minor proteins, become phosphorylated during a cyclic nucleotide independent 'autophosphorylation' reaction. (no Refs)

47. ALTERATION BY PROTEIN A OF THE DISTRIBUTION OF IMMUNE COMPLEXES CONTAINING ANTIGEN OF RETROVIRUS.

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Dept. Microbiology, Univ. Arkansas for Medical Sciences, Little Rock, AR, 72205
Clin Immunol Immunopathol; 24(2):186-193 1982

Protein A (PA) altered significantly the clearance rate and tissue uptake of 125I-p30-anti-p30 immune complexes (IC). 125I-labeled IC formed at equivalence and injected iv into normal Brown Norway rats were localized in the spleen and liver at 10 min and 1 hr, but were sequestered primarily in the spleen thereafter. IC mixed with PA were cleared from the liver by 4 hr and the amount localized in the spleen at 24 hr was reduced 10-fold. PA exerted this effect even if injected 1 min before or after IC. An effect of PA could be observed as early as 4 hr and as late as 8 days after injection. PA also enhanced the whole body elimination of IC during the first 24 hr. In vitro PA did not inhibit binding of antigen to antibody, but did inhibit binding of IC to lymphoid and phagocytic cells. (Author abstract) (42 Refs)

48. ESTABLISHMENT OF FUNCTIONAL, ANTIGEN-SPECIFIC T CELL LINES BY RADLV-INDUCED TRANSFORMATION OF MURINE T LYMPHOCYTES.

Ricciardi-Castagnoli P, Rabbiati F, Barbianti E, Doria G, Adorini L
No affiliation given
Curr Top Microbiol Immunol; 100:89-96 1982

Radiation leukemia viruses (RadLV) were produced by exposing C57Bl/Ka mice to radiation. The RadLv were isolated from the resulting thymomas. T-cell lines containing the viruses were established that secrete antigen-specific products and maintain functional activity in spite of undergoing transformation. RadLV in the T-cell lines are endogenous leukemogenic retroviruses with high oncogenic capacity. RadLV induce neoplastic transformation in target tissues including bone marrow, spleen, thymus, and fetal liver. No transformation of cells of B lineage has not been reported. Antigen-specific T lymphocytes can be infected with RadLV in vitro; transformation occure, however, only if the cells are maintained under conditions which support cellular proliferation. Cells bearing the H-2b haplotype or the Fv-1bb gene are the most susceptible to infection with RadLV; other cell types tend to be resistant to RadLV. Antigen-specific, functional T-cell lines are established by enriching specific T-cells and then infecting them with RadLV. The infected cells are then injected into sublethally irradiated mice, and tumors are allowed to develop. Individual cell lines are produced by cloning. Cells are selected for cloning by means of phenotypic and functional assays. Products of a T-cell line specific for hen egg-white lysozyme (HEL) have been characterized. Since the HEL-specific cells do not suppress a structurally related lysozyme, the specificity of the cells is quite narrow. The specificity is determined by the N-terminal, C-terminal peptide in the HEL molecule. Suppressor activity is restricted by genes located in the H-2 complex and requires identity of the I-J region of the H-2 complexes of the cell factor and its target. (16 Refs)

49. SIMPLE SANDWICH ENZYME IMMUNOASSAY FOR QUANTIFICATION OF MOUSE MAMMARY TUMOR VIRUS IN MOUSE MILK.

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Cancer Lett; 16(2):155-161 1982

Concentration of mouse mammary tumor virus (MMTV) in mouse milk was determined using a sandwich enzyme immunoassay and the optimal conditions of the assay were examined. MMTV was purified from C3H/HeMs mouse milk. A linear dose-response of the enzyme activity bound on the solid phase was observed between 3-1,000 nanogram (ng)/ml MMTV. By using 0.01 M sodium phosphate buffer containing 0.3 M NaCl, 1 milliM MgCl2, 0.1% bovine serum albumin, 0.5% gelatin, and 0.1% NaN3, 10 ng/ml MMTV could be detected in the milk samples. The degree of interference by milk slightly increased with the increase of vol from 0.5-10 ul and was constant over a range of 10-100 ul. The enzyme activity bound onto the solid phase in MMTV samples containing 0.5 and 100 ul milk was approx 60% and 50% of that in MMTV samples suspended in buffer alone, respectively. Results indicated that it is possible to use a wide range of milk vol from various mouse strains. However, 0.5-10 ul MMTV-free milk has to be added to MMTV samples to obtain standard curves. The concentration of MMTV in C3H/HeMs mouse milk ranged from 193-575 ug/ml depending on the animals. When the milk was defatted and cleared by centrifugation, the concentration of MMTV antigens was 57-68% of that in the crude milk samples. (14 Refs)

50. EXPRESSION OF ENDOGENOUS VIRAL GENES IN MOUSE LYMPHOCYTES.

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Curr Top Microbiol Immunol; 98:27-36 1982

The association of expression of endogenous viral genes of xenotropic origin with immunological phenomena in mice and chickens is discussed. Xenotropic murine leukemia virus (X-MuLV) genes are present in all strains of mice. Viral gene products, such as X-MuLV gp70, may be expressed spontaneously or after stimulation by mitogens or antigens. In some strains of mice, stimulation of B-lymphocytes by mitogens

leads to differentiation to immunoglobulin-producing cells, accompanied by production of C-type virus particles. T-cells can also be stimulated to express MuLV gp70 and env gene products. X-MuLV gp70 is expressed to widely varying degrees by lymphocytes from greater than 100 strains of mice studied. Stimulation by B- or T-cell mitogens enhances this expression. In most strains of mice expression of env genes is predominantly repressed. Activation of lymphocytes results in derepression of env genes. Some evidence suggests that gp70 or other X-MuLV gene products may play some role in normal physiological processes in mice and chickens. Several studies indicate that both mouse and chicken proviral sequences have long 5' and 3' terminal repeats (LTR). These LTR are capable of promoting transformation. If X-MuLV viruses have similar promoting activity, LTR may be more important than structural viral genes in promoting growth and/or differentiation of host cells, particularly lymphocytes. (24 Refs)

51. SURFACE ANTIGEN EXPRESSED IN HEMATOPOIETIC CELLS DERIVED FROM FV-4 MOUSE STRAINS.

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Dept. Microbiology, Univ. Tokyo, P. O. Box Hongo, Tokyo 113, Japan
JNCI; 68(6):1005-1009 1982

Fv-4 locus controls the susceptibility of mice to ecotropic murine leukemia virus. Antiserum against Fv-4r/s mice with BALB/c background was raised in inbred BALB/c mice. In the complement-dependent cytotoxicity test, the antiserum killed the hematopoietic cells derived from Fv-4r/- mice but not those from Fv-4s/s mice, and the genetic cross experiments located the locus controlling the expression of the target molecule of the antibody in the close vicinity of Fv-4. In addition, the antigenic expression of the exogenously infecting MuLV suppressed the expression of the target molecule of the antiserum. The expressions of these two antigens appear to compete with each other on the cell surface. (Author abstract) (21 Refs)

IMMUNE RESPONSE TO VIRUS-ASSOCIATED ANTIGENS

52. IMMUNOLOGY AND DIAGNOSIS OF NASOPHARYNGEAL CARCINOMA.

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Excerpta Med Int Congr Ser; 571:389-397 1982

Results of a series of studies are discussed to assess the value of testing for some Epstein-Barr virus (EBV)-specific serologic and immunologic markers in the diagnosis of nasopharyngeal cancer (NPC). All the sera tested were from Chinese patients and residents in Hong Kong. The sera were titrated for IgA and IgG antibodies to viral capsid antigen (VCA) and early antigen (EA) of EBV by the indirect immunofluorescent technique. The first study showed that NPC patients have a broader spectrum and higher geometric mean titer (GMT) of serum antibodies to EBV-specific antigens than do patients with other tumors of the respiratory and upper aerodigestive tracts and healthy subjects. A second study established that there was a stepwise rise in the GMT for all four antibodies with advancing stages of disease (I-IV). A further study was done to assess the value of titration of the four antibodies in the diagnosis of NPC. IgA to VCA had the highest sensitivity with a detection rate of 95% and relatively high specificity. IgA to EA was highly specific with no false positives but a detection rate of only 78%. IgG to VCA was the least discriminatory, while EgG to EA fell between IgA to EA and IgG to VCA. An ongoing study involves the evaluation of the titration of serum IgA to VCA as a screening test for NPC in its early presymptomatic stage in subjects known to have a high risk of the disease, namely, close blood-linked relatives of Chinese NPC patients. In these patients, if the serology is suggestive, multiple nasopharyngeal biopsies are indicated. Data are presented on serum EBV-specific antibody titers in four siblings initially and at time of diagnosis of NPC. (17 Refs)

53. POSSIBLE IMMUNOLOGICAL MECHANISMS IN C-TYPE VIRAL LEUKEMOGENESIS IN MICE.

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Curr Top Microbiol Immunol; 98:85-101 1982

The role of C-type viruses in leukemogenesis in mice is reviewed. The mechanisms by which C-type viruses induce leukemia are distinct from those by which the same type of viruses induce sarcomas. In leukemogenesis the viruses are replication-competent, nontransforming, and do not contain additional cellular pathogenic sequences. Latency periods are longer for leukemia than for sarcomas. Induction of leukemia is associated with acute viremia. Studies in mice indicate cellular immune response is an integral part of the process of leukemogenesis. Among the specific components of the leukemogenic process is the absolute requirement for antigen-specific lymphocytes. Preleukemic states involve chronic immune stimulation that is not limited to antigen-specific components but includes systemic effects. A proposed model suggests that immune stimulation is required to provide targets for viral infection and transformation. A second model describes a unique interaction of virus with antigen-specific cells to produce transformation. In a third proposed model, chronic immune stimulation produces somatic errors, which result in transformation leading to leukemia. Experimental approaches are available for future research to clarify the mechanisms of viral leukemogenesis. (63 Refs)

54. MOUSE NATURAL ANTIBODIES AND NATURAL KILLER (NK) CELLS SHOW SIMILAR SPECIFICITY AGAINST IN VIVO GROWN LYMPHOMA SUBLINES (MEETING ABSTRACT).

Gronberg A, Kiessling R, Eriksson E, Klein GO
Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden
Scand J Immunol; 15(1):131 1982

Serum from young normal (AxC57BL) F1 hybrid mice has been found to contain natural antibodies (Nab) which are cytotoxic to the A strain derived Mo-MLV (Moloney-mouse leukemia virus) induced YAC lymphoma in C-dependent assays. The antibodies were predominantly of IgG class but some activity was also seen in the IgM fraction. The sensitivity of different mouse lymphomas to Nab paralleled their expression of Moloney cell surface antigen (MCSA). Thus, YACIR and YAC462-IR which are immunoselected, low MCSA-expressing sublines of YAC, were found to be resistant to Nab. A viral origin of the target antigen for Nab was suggested since the activity against YAC could be completely inhibited by purified

Mo-MLV. Mouse natural killer (NK) cells were found to show a similar specificity as Nab when tested against in vivo grown lymphomas. YAC showed significantly higher sensitivity to lysis than YACIR and YAC462-IR when ascites grown cells were used as targets. The two immunoselected sublines were also less susceptible than YAC to the in vivo hybrid resistance effect. These data suggest a possible involvement of Nab and/or NK cells in tumor resistance. (no Refs)

55. HUMORAL IMMUNE RESPONSE IN EPSTEIN-BARR VIRUS INFECTIONS. I. ELEVATED SERUM CONCENTRATION OF THE IGG1 SUBCLASS IN INFECTIOUS MONONUCLEOSIS AND NASOPHARYNGEAL CARCINOMA.

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Clin Exp Immunol; 49(1):149-156 1982

Using radial immunodiffusion we measured IgG subclass concentrations and studied their distribution in serum samples from patients with infectious mononucleosis (IM) and nasopharyngeal carcinoma (NPC), two Epstein-Barr virus (EBV)-associated diseases, in comparison with two control groups [completely anti-EBV negative persons and subjects carrying antibodies to the viral capsid antigen (VCA)]. Antibody titers to VCA and to the early antigen (EA) were determined by indirect immunofluorescence and revealed characteristic patterns for the respective diagnostic groups. Nephelometric assays served for quantitating total protein, albumin, total IgG, IgA and IgM in all the sera. In the IM and NPC groups the concentration of IgG1 was significantly elevated by more than 50% whereas the other three subclasses remained unchanged as compared with the controls. Correspondingly, we found a significant increase of total IgG in IM and NPC. In IM, the only disease where VCA-specific IgM antibodies have been reported to occur, IgM leveles were markedly elevated. Our data suggest that the IgG1 subclass plays an important role in the humoral immune response to EBV-determined antigens and that it is possibly involved in the control of virus infection. (Author abstract) (24 Refs)

56. ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX IN RESISTANCE TO VIRAL LEUKEMIA; ITS EFFECT ON THE PRELEUKEMIC STAGE OF LEUKEMOGENESIS.

Lonai P, Katz E, Haran-Ghera N
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Springer Semin Immunopathol; 4(4):373-396 1982

The mechanisms of H-2 linked resistance to viral leukemia in mice are discussed. Localization of H-2 linked resistance loci is described with respect to the H-2 complex and associated mechanisms and localization of the H-2 linked leukemia resistance genes. Studies of the immunologic nature of H-2 linked resistance are reviewed. Mechanisms of H-2 linked immunologic resistance are discussed with respect to the associative recognition of viral and H-2 antigens, a role by humoral immunity, H-2 linked resistance and preleukemic arrest, and changes of H-2 antigen expression on thymocytes following leukemia virus infection. It is suggested that in resistance to leukemogenesis, a number of H-2 loci cooperate, indicating that resistance appears to be the result of interactions between different H-2 controlled mechanisms. Preleukemic lymphocytes may have an important role in the induction of anti-leukemia immunity, which is not, or is less efficiently, induced by autonomously growing leukemia cells. The mechanism of preleukemic arrest may be explained by associative recognition of viral antigens on preleukemic cells. Alternative hypotheses of the leukemogenicity of preleukemic cells in resistant mice are presented. A detailed analysis of thymus subpopulation changes in D-region associated radiation leukemia virus (D-RadLV) and A-RadLV infected C57BL/6 mice is presented. Resistance to leukemogenesis appears to be the result of interactions between different H-2 controlled mechanisms. (99 Refs)

57. PERSISTENT ACTIVE INFECTION OF EPSTEIN-BARR VIRUS (EBV) IN CARRIER FEMALES OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME (XLP).

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Excerpta Med Int Congr Ser; 571:375-379 1982

Among conditions that may follow infection with Epstein-Barr virus (EBV), is malignant lymphoma in males affected by the X-linked lymphoproliferative syndrome (XLP). To test the hypothesis that the variable expression of XLP is manifested in obligate carrier females, blood from 12 obligate carrier females was studied for anti-viral capsid antigen (VCA), anti-early antigen (anti-EA) and anti-Epstein-Barr nuclear-associated antigen (EBNA). All carriers were seropositive to EBV. The reciprocal geometric mean titer for IgG anti-VCA was elevated to 570 in the carrier females compared to 100 in 24 controls. The range of anti-VCA was from 80 to 5,120. IgA class anti-VCA was found in 2/3 of the carriers. All but one of those with anti-VCA of IgA class showed anti-EA, indicative of active infection and immunodeficiency. About one-half of the carriers had persistent anti-EA antibodies. However, the anti-EBNA levels of carrier females were similar to those of the healthy controls. There was no apparent relationship between IgM level and EBV-specific antibody titers. The paradoxically elevated EBV-specific antibodies which tend to persist in obligate carriers of XLP provides an opportunity to define the immunopathology of XLP and to detect carrier females. (17 Refs)

58. IMMUNOTHERAPY IN NUDE MICE OF HUMAN HEPATOMA USING MONOCLONAL ANTIBODIES AGAINST HEPATITIS B VIRUS.

Shouval D, Shafritz DA, Zurawski VR, Isselbacher KJ, Wands JR
Liver Res. Center, Dept. Medicine and Cell Biology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Nature; 298(5874):567-569 1982

The ability of (IgM, IgG2a, and IgG1) monoclonal antibodies (anti-HBs) to hepatitis B surface antigen to specifically prevent or suppress tumor formation in a substantial number of animals was examined in athymic nude mice injected with the human hepatoma cell line PLC/PRF/5. Treated BALB/c male nude mice received IgM anti-HBs (iv), IgG2a anti-HBs (ip), or IgG1 anti-HBs (ip) and control mice received 100 ul of phosphate-buffered saline iv or ip. Sc injection of PLC/PRF/5 cells produced tumors in 37/39 control nude mice. Treatment of tumor-injected mice with anti-HBs IgM prevented tumor formation in 15/23 animals, and suppressed tumor growth in 4 others. Anti-HBs IgG2a showed a protective response in 18/26 animals, with prevention of tumor formation in 8 mice and suppression of tumor growth in 10 mice. Monoclonal IgG1 anti-HBs, which bound effectively to PLC/PRF/5 cells in culture, had no effect on tumor growth. No response was observed in 11/16 tumor-injected mice who were treated with monoclonal antibodies to non-hepatitis B virus. Further evidence for sup-

pression of tumor growth by monoclonal anti-HBs IGM or IgG2a was shown by an increased tumor latency, a slower tumor growth rate, and a decreased tumor wt at necroscopy compared to control animals. Differences in the effectiveness of the three monoclonal antibodies on PLC/PRF/5 tumor growth are discussed. (20 Refs)

59. NATURAL AND INDUCED IMMUNITY TO MOUSE MAMMARY TUMORS AND THE MAMMARY TUMOR VIRUS (MUMTV).

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Springer Semin Immunopathol; 4(4):333-372 1982

Information on immune responses in normal and tumor-bearing hosts either against murine mammary tumor virus (MuMTV) antigens or the actual tumors themselves is discussed and correlation with the possible prophylaxis and therapy of tumors in the mouse mammary tumor model system is made. The cell-mediated immune responses (mostly those mediated by T cells), which can be detected in vivo or in vitro either spontaneously or in immunized mice are reviewed in detail. The unique properties of the MuMTV model and in vivo immunologic studies are discussed. Topics discussed include in vitro cytotoxicity and related phenomena (studies using colony-inhibition assays and microcytotoxicity, antigenic complexities of the system) and studies using cell-mediated cytotoxicity assays (specificity and characteristics of the response, in vivo-in vitro discrepancies, serum factors, T cell interactions, suppressor T cells in MTV-positive mice, the effect of thymectomy, in vitro sensitization, natural cell mediated cytotoxicity in MTV-positive mice and horizontal transmission of MuMTV). Adult thymectomy completely abrogated the suppressive activity in the Lyt-23 fraction of MTV-positive cells, but had no effect on the Lyt-1 helper component. These findings may explain the in vivo effects of thymectomy producing a decline of mammary tumors. Thymectomy at 6 days of age produced a significant decrease in tumor incidence, while thymectomy after 30 days of age had no effect on mammary tumor development in C3H/BiUmc virgin females. (247 Refs)

60. IMMUNOPATHOLOGY OF POLYOMA-INDUCED TUMORS.

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Springer Semin Immunopathol; 4(4):317-332 1982

Studies on the immunologic aspect of the polyoma (Py) virus tumor model are reviewed. The Py virus is discussed with respect to its history and structure. Two types of Py virus-cell interaction has been reported. In one type, in vitro mouse cells undergo predominantly a productive (lytic) infection leading to production and release of progeny virus and destruction of the host cell. In the other type, the virus transiently induces a small number of divisions and phenotypic alterations (abortive infection); only a small percentage of the infected cells undergo transformation. These stable transformants contain integrated viral DNA. Antigens associated with Py-transformed cells include those mainly located in the nucleus (T-antigens) and those associated with the cell membrane [tumor-specific transplantation antigens (TSTA) and tumor-associated surface antigen(s) (TASA)]. TSTA are thought to play a major role in host resistance to cancer. The relationship between the Py TSTA and the other Py antigens (T-antigens and TASA) is unclear. Immune reactions are discussed with respect to in vivo assays (immunodepression and Py oncogenesis and passive transfer of immunity by sensitized lymphoid cells) and in vitro assays (colony-inhibition assay, microcytotoxicity assay, cytotoxicity assay using radioisotopes). T-cell dependent mechanisms appear to play a crucial role in resistance against the development of Py virus induced tumors. (102 Refs)

61. IMMUNE STIMULATION OF SENSITIZED CHICKEN LYMPHOCYTES BY AVIAN RETROVIRUS PROTEINS.

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J Gen Virol; 60(part2):391-395 1982

Peripheral blood lymphocytes of chickens bearing tumors induced by avian sarcoma virus can be specifically stimulated to divide by the crude culture fluids of virus-infected cells. In this communication, we show that relevant antigenic activity apparently resides in each of the internal virus proteins p15 and p27. The ability of infectious culture fluids to be mitogenic for sensitized lymphocytes is greatly reduced following treatment with antibodies specific for either total avian myeloblastosis virus (AMV) protein or for p27. (Author abstract) (14 Refs)

62. RETROVIRUS LYMPHOMAGENESIS: RELATIONSHIP OF NORMAL IMMUNE RECEPTORS TO MALIGNANT CELL PROLIFERATION.

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Curr Top Microbiol Immunol; 98:103-112 1982

The hypothesis that the principal reason for proliferation of cells transformed by slowly transforming retroviruses is due to stimulation by their antigen-specific receptor-mitogen complex is proposed. The oncogene should be the viral env gene, not a host cellular gene. Experimental evidence is reviewed which illustrates the following: each T cell lymphoma expresses surface receptor highly specific for the retrovirus which is produced by it; receptor recognition specificity maps to the env region; the virus receptor is a marker for leukemia cells and distinguishes them from preleukemic cells in the same thymus; virus receptor binding may regulate lymphoma proliferation; and virus receptors on lymphoma cells can be antigen-specific receptors. Taken together, the results provide strong evidence for a receptor-mediated leukemogenesis hypothesis (RMLH). A comparison of this hypothesis with the chronic immunostimulation hypothesis (CIH) demonstrated the following differences: CIH requires a second genetic event within the stimulated host cell before lymphoma generation can occur, while RMLH does not; in CIH, the preleukemic cells switch from antigen-responsive behavior to growth factor-responsive behavior; with CIH the proliferating cells in the preleukemic period appear to be responsive to gp70, while the RMLH model indicates a specificity controlled by sequences within p15E and/or the R region; and CIH concerns mitogen responsiveness of the spleen population, while RMLH follows receptor binding specificities of thymus cells and intrathymic lymphomas. (21 Refs)

EFFECTS OF ENDOGENOUS/ EXOGENOUS AGENTS ON VIRUS-ASSOCIATED ANTIGENS

63. REPLICATION OF EPSTEIN-BARR VIRUS DNA IN LYMPHOBLASTOID CELLS TREATED FOR EXTENDED PERIODS WITH ACYCLOVIR.

Colby BM, Shaw JE, Datta AK, Pagano JS
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Am J Med; 73(1A):77-81 1982

An Epstein-Barr virus (EBV)-producing human lymphoblastoid cell line (P3HR-1) was characterized after prolonged exposure to 9-(2-hydroxyethoxymethyl)guanine (acyclovir). P3HR-1 cells grown for 11 mo in the presence of acyclovir had the same number of EBV genomes (approx 15/cell) as did short-term acyclovir-treated cells. After removal of the drug, the number of EBV genome equivalents of long-term acyclovir-treated cultures (15/cell) returned to P3HR-1 control levels (340/cell). Indirect immunofluorescence studies demonstrated reduced percentages of long-term (6 to 12 mo) acyclovir-treated P3HR-1 cells expressing both EBV early antigens (EA) and viral capsid antigens (VCA). This contrasts with short-term acyclovir-treated cultures where EA is expressed at normal levels even though VCA expression is reduced. Restriction fragment patterns of the total EBV DNA from both short- and long-term acyclovir-treated cultures were identical with the exception of two fragments present in short- but not long-term acyclovir-treated cultures. EBV-associated DNA polymerase was present in long-term acyclovir-treated cultures with the level of activity, as determined by assay in vitro, comparable to that in untreated P3HR-1 cells. The polymerase activity in the treated cells was sensitive in vitro to acyclovir triphosphate, N-ethylmaleimide (NEM), and phosphonoacetic acid (PAA). These studies demonstrate that acyclovir inhibits the EBV-productive cycle in P3HR-1 cells continuously during extended periods of treatment. (Author abstract) (21 Refs)

64. ACTIVATION OF EPSTEIN-BARR VIRUS EXPRESSION IN HUMAN LYMPHOBLASTOID P3HR-1 AND RAJI CELLS WITH PROPIONIC ACID AND WITH CULTURE FLUIDS OF PROPIONIC ACID-PRODUCING ANAEROBES.

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Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Cancer Lett; 16(2):117-120 1982

Epstein-Barr virus (EBV) expression was studied in EBV genome-carrying cells (P3HR-1 and Raji) cultured with four species of propionic acid (PA)-producing microbes (Propionibacterium acnes, Propionibacterium avidum, Propionibacterium lymphophilum, and Arachnia propionica) commonly isolated from mouth, skin, and intestinal tract of man. After 48 hr, 20-40% of the cells were EBV-early associated (EA) positive and 15-20% were virus capsid antigen positive as assayed by indirect immunofluorescence assay. EBV inducing capacity appeared to correlate with the fatty acid content in the culture fluid. PA per se was assayed for the capacity to induce EBV-associated antigens. EBV inducing activity of P3HR-1 cells was observed at PA concentrations greater than 10 mM. In non-producer Raji cells, PA combined with croton oil (CRO) or n-butyrate enhanced induction of EA. The EBV-inducing capacity of PA in non-producer Raji cells when used with CRO, a tumor promoting agent, is interesting from the point of view of skin carcinogenesis. The role of PA-producing microbes of normal cutaneous flora, P acnes in particular, in the neoplastic process is not known. (9 Refs)

65. EFFECT OF ACYCLOVIR ON HERPES SIMPLEX VIRUS REPLICATION IN A PERSISTENTLY INFECTED HUMAN LYMPHOBLASTOID CELL LINE (P3HR-1).

Shaw JE, Colby BM, Leong J, Bolling TJ
Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Am J Med; 73(1A):72-76 1982

We examined the effect of acyclovir on herpes simplex virus (HSV) replication in the persistently infected human lymphoblastoid cell line, P3HR-1. During 10 days of continuous exposure of P3HR-1 cells to 100 uM acyclovir there was a decrease in the number of cells expressing HSV antigens, the number of copies of HSV DNA per cell, and the infectivity of extracellular virus. A significant increase in each of these was detected after 14 days of continuous exposure of P3HR-1 cells to the drug, demonstrating that the replication of HSV has become resistant to inhibition by acyclovir. No apparent resistance of EBV replication to inhibition by acyclovir, however, was detected in HSV-infected P3HR-1 cells. The number of copies per cell of EBV and HSV DNA increased after exposure of HSV-infected P3HR-1 cells to the tumor promoter TPA (12-O-tetradecanoyl-phorbol-13-acetate). When cells were exposed continuously to acyclovir for 4 mo and then exposed to acyclovir and TPA simultaneously, the number of copies per cell of HSV DNA increased, but the number of copies per cell of EBV DNA increased by only a few, if any. The detection of P3HR-1 cultures of individual cells expressing both HSV and EBV antigens suggested that HSV and EBV productive cycles could occur simultaneously within the same cell. However, single cells very rarely expressed both antigens simultaneously. (Author abstract) (19 Refs)

OTHER RELATED STUDIES

66. PERSISTENT POLYCLONAL LYMPHOCYTOSIS OF B LYMPHOCYTES.

Gordon DS, Jones BM, Browning SW, Spira TJ, Lawrence DN
Div. Host Factors, Center for Disease Control, 1600 Clifton Road, Atlanta, GA, 30333
N Engl J Med; 307(4):232-236 1982

Three patients (females, 41-54 yr old) with a unique stable lymphoproliferative disease of uncertain cause, distinct from typical monoclonal malignant lymphoid proliferations, are described. All patients have had relative and absolute lymphocytosis or persistent atypical lymphocytes or both for 8-15 yr. All have had binucleated lymphocytes on numerous occasions. The lymphocytosis was clearly of the B-cell type. Representation of both kappa and lambda light chains was evident, indicating a polyclonal expansion of the B-lymphocyte pool. T cells, as well as helper and suppressor T-cell subsets, were normal. Uniformly low levels of IgG and IgA and uniformly high levels of IgM were noted in serum samples. Patients were either homozygous for HLA-DR7 or DR7/blank. It is unlikely that these three caucasian patients could have DR7 as the sole detectable DR antigen by chance alone. Morphology of the lymphocytes strongly suggested a viral pathogenesis. However, preliminary attempts to isolate a virus or document viral antigens on peripheral cells of these patients were unsuccessful. (35 Refs)

67. EXPRESSION OF MURINE H-2KB HISTOCOMPATIBILITY ANTIGEN IN CELLS TRANSFORMED WITH CLONED H-2 GENES.

Mellor AL, Golden L, Weiss E, Bullman H, Hurst J, Simpson E, James RF, Townsend AR, Taylor PM, Schmidt W, Ferluga J, Leben L, Santamaria M, Atfield G, Festenstein H, Flavell RA

Lab. Gene Structure and Expression, Natl. Inst. Medical Res., The Ridgeway, Mill Hill, London NW7 1AA, England

Nature; 298(5874):529-534 1982

Cosmids containing H-2 histocompatibility antigen genes of the H-2b haplotype have been isolated. One of these genes expresses a 45,000 mol wt protein, indistinguishable from H-2Kb when introduced into mouse L cells. These H-2Kb transformed L cells can be killed by allospecific anti-H-2Kb cytotoxic T cells. Moreover, when infected with influenza virus, they can be killed by an H-2Kb-restricted, influenza virus-specific cytotoxic T cell line. These results show that expression of the H-2Kb gene product on the L-cell surface is sufficient to make it a target for specific T-cell killing. (Author abstract) (26 Refs)

68. IDENTIFICATION OF AN ONCOFETAL ANTIGEN (GP90) ON MURINE B16 MELANOMA CELLS.

Nishio C, Ishii Y, Ishii K, Kikuchi K
(c/o Ishii) Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan

Eur J Cancer Clin Oncol; 18(6):579-588 1982

A xenoantiserum to murine B16 melanoma cells was developed by immunizing rabbits with cultured B16 melanoma cells. This antiserum could, after extensive absorption with normal C57BL/6 mouse tissues, react with syngeneic (B16) and allogeneic (HP) melanomas as well as with other murine neoplasms, including syngeneic 75S adenocarcinoma, allogeneic myeloma and leukemic T cell lines. The antiserum also cross-reacted with syngeneic fetal fibroblasts and with an allogeneic fetal fibroblast cell line (SC-1) either uninfected or infected with murine leukemia virus (MuLV). Immunoprecipitated material from B16 melanoma cell-surface glycoproteins that had been labeled with [125I] by lactoperoxidase and purified by a Lentil lectin column was analyzed by one-dimensional SDS- and two-dimensional polyacrylamide gel electrophoresis, which disclosed an acidic glycoprotein with a molecular weight (mol wt) of 90 K daltons. Absorption studies suggested that the 90 K mol wt glycoprotein represented the oncofetal moiety expressed in murine melanoma, carcinoma and fetal tissues. When the amount of this antigen in developing C57BL/6 mouse fetuses was measured by absorption assays, we found that it was expressed strongly in those fetuses just before birth. Binding and absorption studies demonstrated that the 90 K mol wt glycoprotein, while being expressed on a variety of fetal and neoplastic cells in mice, did not exist at detectable levels in normal tissues of adult C57BL/6 mice, including tissues of the thymus, lymph node, spleen, liver, brain, lung and kidney. (Author abstract) (26 Refs)

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